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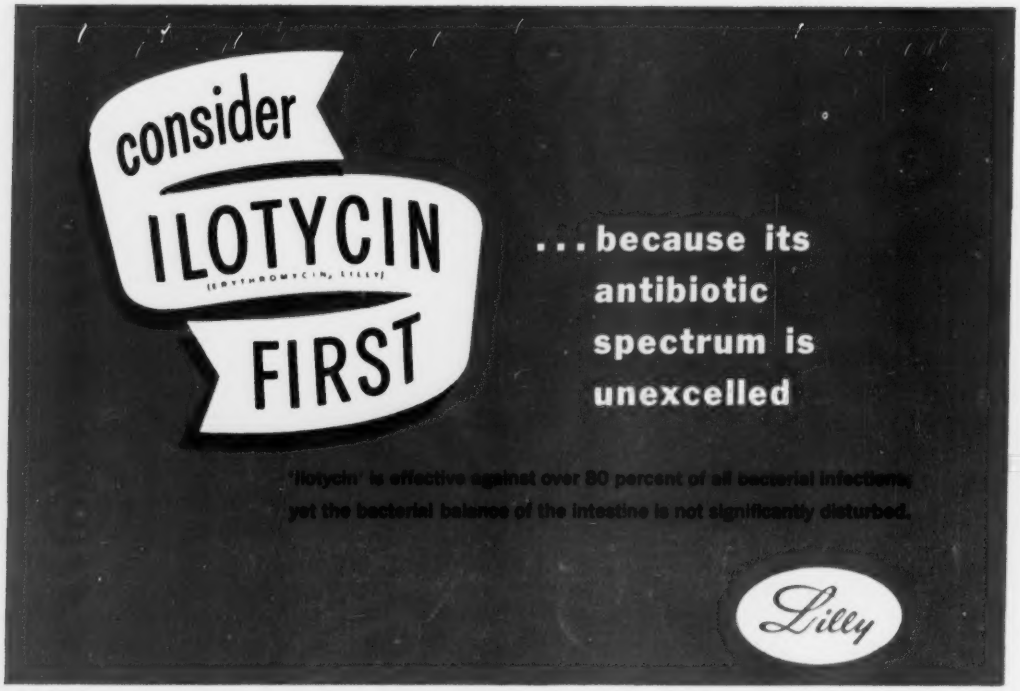
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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

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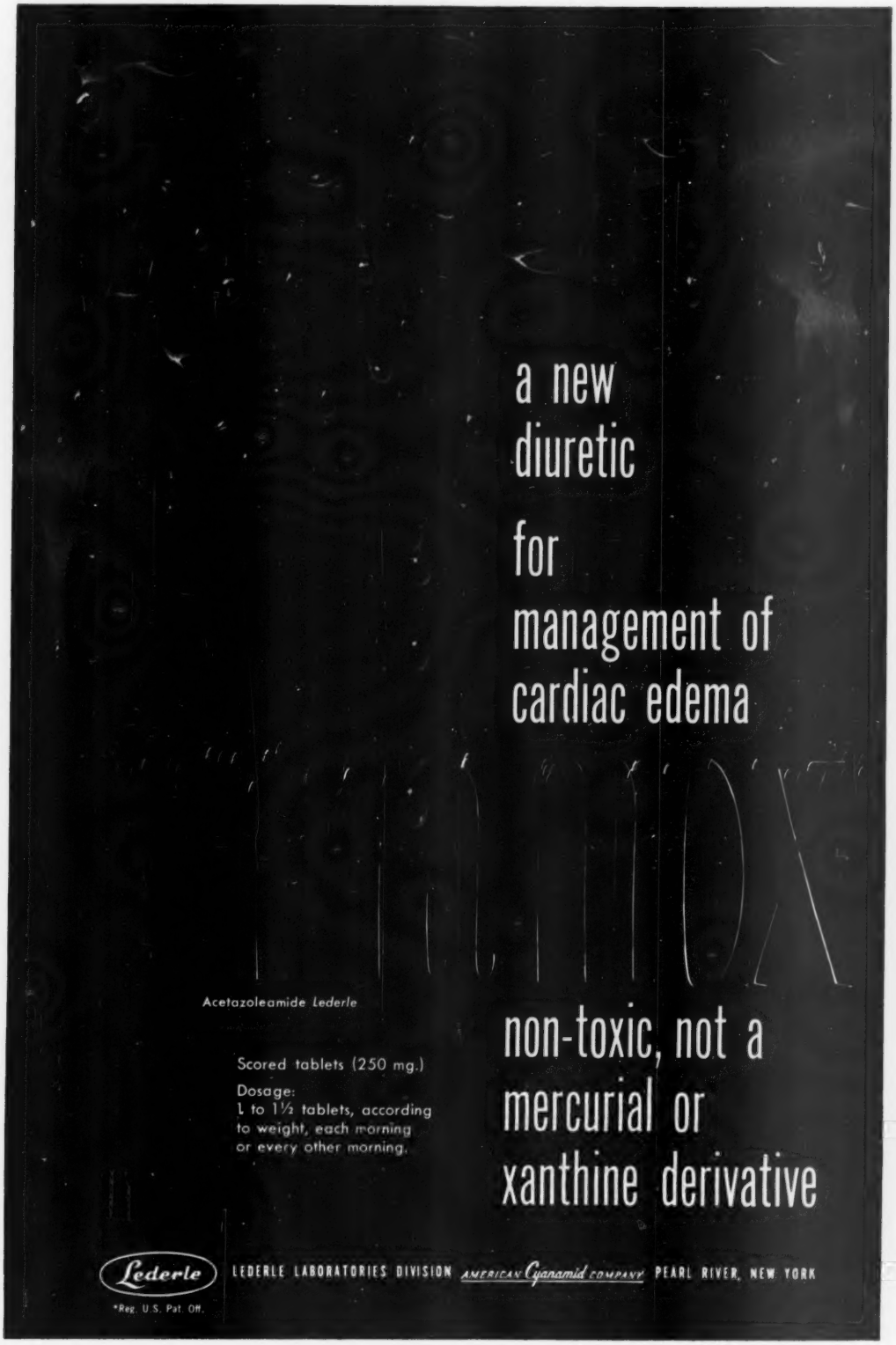
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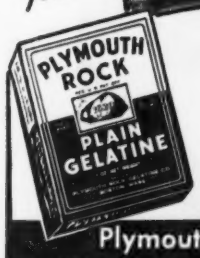

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Volume 251 OCTOBER 21, 1954 Number 17

MISSED DIAGNOSES IN HEAD AND NECK TUMORS*

G. David King, M.D.†

BOSTON

In spite of the tremendous emphasis that has been placed on the problem of tumors in recent years, many patients still are denied an opportunity for cure because of a missed diagnosis. A clinical impression has been gained in the past five years, from work with a large group of patients with head and neck tumors, that mere carelessness was not the only reason that certain tumors were overlooked and others obviously present remained undiagnosed. Because of this impression, the records of a number of patients were analyzed in an attempt to ascertain whether there were common grounds of error that were correctable. The results of that analysis are the basis of this communication. No attempt was made to reach any statistical conclusions regarding missed diagnosis of certain tumors a certain percentage of the time because this did not appear to clarify the problem but rather a number of errors common to all or several of these tumors was discovered, and these are considered below.

Material

For this study the records of all new patients, 370 in number, with various head and neck tumors seen in the Department of Otolaryngology at the Lahey Clinic during 1952 and 1953 were analyzed.

A missed diagnosis was a significant factor in the final outcome of more than 25 per cent, either because the disease had progressed so far that curative treatment could not be employed or because the magnitude of treatment and the prognosis had been greatly altered. Delay is the arch enemy of the therapist. The catastrophe of a diagnostic error is delay. For example, in this group, 11 patients were treated for cancer of the tongue less than 2.5 cm. in diameter without cervical metastases. There has been only 1 case of progression of disease among these patients with follow-up periods ranging from six to twenty-four months. On the other hand, 12 patients with large cancers of the tongue were treated during the same period. Nine of these have already died of their disease.

Blind Areas

The greatest number of mistakes occurred in relation to blind areas. To the examiner who does not use a head light, speculums, retractors and mirrors, the internal epithelium of the nose, nasopharynx, larynx and subjacent upper trachea, posterior tongue and hypopharynx is invisible. Even the most elaborate indirect examination cannot be substituted for adequate inspection of a questionable area.

The remedy for this failing is for the physician to become proficient in the examination of the internal epithelium. If he is not, he must consult someone who has the necessary skill. Ability to make this examination will benefit the physician and his patient and by persistence can be acquired in daily practice.

Cervical Lymphadenopathy

A second common source of error concerned misinterpretation of enlarged cervical lymph nodes. True cervical adenitis is due to extension of bacterial infection along lymph-drainage pathways from the tissues of the head or neck. The commonest cause of enlarged lymph nodes in the neck in the absence of bacterial infection is metastatic disease from the epithelium of the head or neck and frequently from the blind areas mentioned above. Supraclavicular cervical lymph nodes are involved with metastatic spread from cancer of the thyroid gland, lung, breast, esophagus and stomach. Lymphoma of cervical lymph nodes is common.

The proper management of an enlarged cervical lymph node may require all the personal and technical resources of the physician so that a diagnosis can be made and proper treatment given. The history must be thorough, and, most important, one must consider the possibility of cancer that may have been controlled by surgery or radiation even though many years may have elapsed since treatment was given. The general examination, the examination of the internal epithelium and the indicated x-ray and endoscopic investi-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1954.
From the Department of Otolaryngology, Lahey Clinic.

†Otolaryngologist, Lahey Clinic; associate otolaryngologist, New England Baptist and New England Deaconess hospitals.

gations should be carried out. Laboratory studies are often needed and may include blood serologic tests, hematologic and exfoliative cytology and all the tuberculosis tests. Lastly, a biopsy of the cervical lymph node should be performed when the diagnosis still remains in doubt. If a biopsy specimen must be resected from a node adherent to the internal jugular vein, definitive dissection later will have less chance of success. Before such a diagnostic procedure is done, the surgeon should be as certain as possible that curative neck dissection will not be part of the treatment.

Neck dissection for bulky lymphomatous disease and cervical metastatic disease without control of the primary lesion is rarely justifiable. Six patients in the series were so treated before coming to the attention of the Department of Otolaryngology. In 4 of these cases the primary lesion had never been found.

Multiple Primary Carcinoma

Multiple primary carcinomas also constitute a source of error, probably because of a general unawareness of the frequency of their occurrence. Slaughter, Southwick and Smejkal,[1] in an excellent study of intraoral carcinoma, demonstrated that 11 per cent of 783 patients had multiple primary carcinomas in the oral cavity. They pointed out that the entire oral epithelium may show diffuse precancerous growth before specific cancer occurs. Warren and Ehrenreich[2] reported multiple primary carcinomas in 6 per cent of 3900 autopsies on patients who had died of cancer. They estimated that the incidence of multiple primary carcinomas was eleven times greater than would be expected by chance alone, and they concluded that certain persons have a marked susceptibility to tumor formation not only in single systems but in several.

Case 1. A 57-year-old man came to the clinic because of dysphagia, which had been present for 3 weeks. Examination revealed a mass in the hypopharynx. The biopsy diagnosis was epidermoid carcinoma, Grade 3. Supervoltage x-ray therapy was given. The patient was well for 9 months, after which symptoms of dysphagia recurred. Examination did not reveal definite tumor, but there was considerable edema and radiation reaction of the soft tissues of the hypopharynx. It was thought that persistent disease was present. Gastrostomy was performed, from which the patient did not recover. At autopsy the hypopharynx was found to be free from disease. The obstruction was the result of a primary carcinoma of the middle third of the esophagus.

Case 2. A 56-year-old man underwent laryngectomy and staged bilateral radical neck dissection for a subglottic carcinoma with cervical metastases. A short time after the final operation the liver became enlarged, and osteolytic processes developed in the vertebras. Death occurred shortly thereafter. At autopsy no residuum of the primary laryngeal carcinoma was found, but there were extensive hepatic and bony metastases from a primary carcinoma of the body of the pancreas.

It is not suggested that these 2 patients would have been cured if the correct diagnosis had been made, but it is quite possible that a second primary cancer can be managed as successfully as an original primary lesion. Under these circumstances a patient who would otherwise have been saved may easily be lost. The physician's duty is to be aware of the diagnosis so that the best care can be given at all times.

Persistent and Metastatic Disease

Ewert[1,3] recently reported a case of primary renal-cell carcinoma with a solitary pulmonary metastasis; nephrectomy and pneumonectomy were performed, and the patient was alive and well four years after operation. By aggressive treatment of persistent and metastatic disease, certain cases will be salvaged, and this fact should be kept in mind.

The physician who is responsible for the periodic examination of patients who have been treated for cancer should assume that any deviation from health is due to persistent or metastatic disease or a second primary tumor. At the follow-up visit an interval history including all systems should be obtained. The local area and regional lymphatic system should be thoroughly examined. X-ray and special examinations should be carried out as indicated. Patients should be seen frequently enough to minimize the possibility that a situation will develop and become uncontrollable between visits.

Follow-up examination of patients who have had cancer is one phase of medical practice in which the excellent patient-doctor relation that obtains because of the patient's gratitude may be detrimental. When the follow-up visit becomes a social event, a currently resectable lymph node may be attaching itself inseparably to the carotid artery, or a small second primary lesion may be overlooked.

Lymphoma

Lymphomas occur anywhere in the body. Even when the tumor is in such a location that it can be seen, it can easily be confused with infection, with the result that the underlying pathologic process is missed entirely.

Case 3. A 53-year-old woman was admitted to the New England Deaconess Hospital on January 2, 1953, with a 4-month history of a progressive indurated swelling in the right nasolabial fold (Fig. 1). She had been seen by numerous consultants. Extensive laboratory studies and several biopsies from the lesion had led only to the conclusion that this was an obscure inflammatory disease. Examination showed a swelling extending through the entire thickness of the lip, involving the buccal and gingival mucous membranes. An enlarged lymph node was palpable in the right submaxillary triangle, and a roentgenogram of the chest revealed slight widening of the superior mediastinum. A lymphoma was strongly suspected, and a biopsy specimen taken at the periphery of the swelling, well away from the large, central, necrotic area, was diagnosed as reticulum-cell sarcoma. Supervoltage radiation therapy was given, with complete clearing of the lesion on the face and disappearance of the enlarged submaxillary lymph node, but widespread mediastinal and abdominal sarcoma developed and the patient died 2 months after completion of treatment.

This case illustrates several points. In the first place lymphoma, when exposed to infection, will break

down early and resemble infection alone. Secondly, a biopsy specimen from this type of lesion must be taken as far away from the area of infection as possible. These tumors are reticular and not epithelial, and bodily response to infection that is also reticular obscures the characteristic picture. The pathologist may be absolutely unable to make the diagnosis from an infected or necrotic specimen. Thirdly, lymphomas are not hopeless tumors, as the prompt response of this woman's localized lesion demonstrates. Some of these patients can be saved if treatment is begun when the disease is still localized.

Negative Biopsies and Cytologic Studies

Biopsy, more than any other procedure, can be said to be the last word in diagnosis. It is extremely important that any biopsy in a case of suspected neoplastic disease be taken with a considerable amount of thought and with supervision of its processing. Frequently, patients are referred with an accompanying

Figure 1. *Reticulum-Cell Sarcoma of the Right Nasofacial Fold.*

abstract stating that one biopsy or several biopsies have been negative. Yet an obvious, progressive lesion is present. A negative biopsy can never be relied on in such a case. It indicates only that the tissue examined does not contain the pathologic entity. It may have been taken too superficially or too deeply, from near the growth or not near it, or from necrotic material that does not show the characteristic picture. Only a positive biopsy is to be considered diagnostic. Negative biopsy has been an important factor in the delay of curative treatment in this series of patients. It has also been observed that the same reliance has been placed on negative Papanicolaou smears, and this is becoming increasingly common. Here, again, a negative cytologic study does not rule out serious disease. The attempt to obtain positive confirmation of the clinical impression must continue.

Skin Cancer

Skin cancers made up the greatest number (120 cases) of tumors in this series. The comparative indolence of many of these cancers led the first or sec-

Figure 2. *Extensive Carcinoma of the Scalp of Hair-Matrix Origin that Followed Repeated Inadequate Surgical and Radiation Therapy.*
Pulmonary metastases are present.

ond physician consulted into an attitude of complacency. Inadequate therapy, by means of electric needles, chemical agents, improper radiation and surgical operations, was often applied over long periods (Fig. 2). This led to a great deal of unnecessary delay and in 3 cases to a fatal outcome. Cutaneous malignant melanoma, the most insidious and fatal skin cancer, can be cured by early, wide excision. The physician should be alert in assuming that any pigmented area on the body that causes even the slightest suspicion of having changed color, grown larger or altered its biologic activity in any way is a malignant melanoma until proved otherwise. Almost all skin cancers are readily curable if recognized promptly and treated adequately. Surgical intervention or administration of radiation by an experienced physician is the formula for success.

Hemangioma

Hemangioma was found to be a fertile field of mis-

diagnosis. A bright tumor, which on the skin of an infant would not have been a problem to any physician, was frequently missed when it made a sudden appearance in an adult. Hemangiomas, it must be remembered, can appear at any age.

CASE 4. A 32-year-old woman was first seen in September, 1953, with the complaint of progressive swelling, tenderness and discoloration in the right nasofacial fold of 4 years' duration (Fig. 3). Operations had been performed in 1951 and 1952, and early in 1953 sandpapering had been done. Examination of the area showed a localized, red-blue swelling, which could be completely emptied by pressure and which refilled promptly when pressure was released. The diagnosis of a subcutaneous hemangioma was made. It was possible to excise this tumor completely, with a good result.

FIGURE 3. *Subcutaneous Hemangioma Distorting the Overlying Skin.*

Three operative procedures on the skin had failed to improve the basic abnormality.

Two indispensable keys to the diagnosis of hemangiomas are color and compressibility. If these tests are given to a doubtful tumor a prompt answer is usually obtained.

THYROID ENLARGEMENT

The thyroid gland is an important structure that must receive consideration in any case of obscure cervical tumor or symptoms. Benign enlargement seldom causes symptoms unless the enlargement is extreme or the gland happens to be located intrathoracically. Cases have been seen in which thyroid adenomas have been removed as a possible cause of neck symptoms when the adenoma itself was quite innocent. Pain or obstructive symptoms in the air or food passages are probably not due to benign thyroid disease. On further search, which is always indicated, a more serious cause may be found — usually a cancer of the hypopharynx or upper esophagus or of the thyroid gland itself.

SUMMARY AND CONCLUSIONS

A study of 370 patients with tumors of the head and neck seen in the Department of Otolaryngology at the Lahey Clinic in 1952 and 1953 is reported. It was found that diagnostic errors could to some extent be classified. On the basis of these findings, a clearer approach to some of these problems can be hoped for.

The commonest causes of missed diagnoses were as follows: failure to make a competent examination of the internal epithelium of the head and neck; misinterpretation of cervical lymphadenopathy; lack of awareness of the common occurrence of second primary persistent and metastatic disease; confusion of lymphoma with infection; unjustified optimism regarding the benignancy of skin lesions; atypically located hemangiomas; undue reliance on negative biopsy reports; and misinterpretation of thyroid enlargement.

The information program that the American Cancer Society and similar agencies have been conducting for the past few years has made great progress in bringing patients with tumors into the hands of doctors at a much earlier time. The patients, moreover, are much more willing to undergo adequate treatment for their disease when it is made clear to them that this is necessary. An attitude of complacency, watchful waiting or wishful thinking on the part of the physician permits neoplastic disease to progress to the untreatable stage, in many cases very rapidly. Missed diagnosis delays the definitive treatment. The successful treatment of head and neck tumors depends on early diagnosis and prompt, adequate treatment.

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DIETARY PROTEIN IN THE GENESIS OF HEPATIC COMA*

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IN the past decade the therapy of severe liver disease has been directed toward the provision of a high or adequate protein and caloric intake.[1,2] A syndrome resembling impending hepatic coma has been observed to follow the administration of certain nitrogenous substances to some patients with severe cirrhosis of the liver.[3,4] This has resulted in an increased awareness of the intolerance of patients to these materials, including dietary protein.

This communication describes 3 additional patients with chronic alcoholism, cirrhosis of the liver and neurologic complications who manifested an intolerance to the administration of dietary protein and on whom the provision of protein may have had an adverse effect.

METHODS AND RESULTS

The patients were observed on the medical wards of the Boston City Hospital. Biochemical studies were made in the Thorndike Memorial Laboratory by technics previously reported.[5,6] The clinical syndrome of impending coma, as described by Adams and Foley,[7] consists of the presence of a characteristic "flapping" tremor, best observed with sustained posturing of the outstretched arms and hands, and drowsiness, confusion and disorientation. Semicoma refers to stupor or a state of unconsciousness from which the patient can be partially aroused. Coma refers to unconsciousness from which the patient cannot be aroused or in which he does not respond to painful stimuli. The electroencephalographic patterns¶ from patients with hepatic coma, previously described by Foley, Watson and Adams,[8] consist of bursts of bilaterally synchronous slow activity, 2 or 3 per second in frequency, occurring predominantly in the frontal areas.

CASE REPORTS

CASE 1. J.M., a 67-year-old man with chronic alcoholism, was admitted to the Thorndike Metabolic Ward for the 2d time on December 26, 1952, because of anorexia, "difficulty with swallowing" and the onset of a "flapping" tremor 10 days before. During the 1st admission, from May 27 to August 2, a diagnosis of cirrhosis of the liver with ascites and edema had been established. The patient had previously required 5 abdominal paracenteses; however, ascites formation had been arrested when a diet providing 10 milliequiv. of sodium daily was instituted. At no time had an abnormality in mental status, a "flapping" tremor or other neurologic disturbance been noted during the 1st admission. Some improvement in liver function had occurred, as evidenced by decreases in total serum bilirubin, thymol turbidity, urinary urobilinogen and urinary bile. Bromsulfalein retention in 45 minutes declined from 46 to 39 per cent.

In the interval from August 2 to readmission he was observed as an outpatient. During this interval he abstained from alcohol ingestion and had an adequate diet restricted in sodium until 2 months before readmission, when his intake as estimated from dietary history fell to 1000 calories per day, consumed mainly as a low-sodium milk substitute and other liquids because of difficulty with glutition. An upper gastrointestinal series revealed esophageal varices but no other abnormality. After a period during which a higher intake of calories and proteins was recommended, he became somnolent, depressed and developed a "flapping" tremor.

Physical examination showed a co-operative but somewhat lethargic and depressed man who weighed 81.7 kg. There were a few spider angiomas, minimal palmar erythema, moderate gynecomastia, enlarged collateral abdominal veins, moderate ascites and ankle edema. The liver and spleen were not palpable. Positive neurologic findings included generalized muscle weakness and a definite "flapping" tremor on sustained posturing of the outstretched hands. In addition, marked rhythmic contractions of the forearm muscles occurred when the patient firmly grasped the examiner's hand. He was somewhat slow in response to questioning, but oriented in time and place.

The temperature was 98.6°F., the pulse 88, and the respirations 16. The blood pressure was 110/65.

Initial laboratory examination indicated a moderate anemia (hemoglobin of 8.8 gm. per 100 cc. and hematocrit of 29 per cent). Bromsulfalein retention after 45 minutes was 46 per cent, and the serum bilirubin 0.85 mg. (1 minute) and 2.7 mg. (total per 100 cc.), and thymol turbidity 1.5 MacLagen units, thymol flocculation was negative, urinary urobilinogen was positive at a dilution of 1:64, and urinary bile was negative.

There was no observable significant variation in the degree of liver impairment as judged clinically and by laboratory tests throughout the hospital course. The hematocrit gradually declined from 28 to 25 per cent; the total serum bilirubin varied from 2.8 to 1.8 mg. per 100 cc., the thymol turbidity from 1.5 to 2.5 MacLagen units, and thymol flocculation from 0 to +. The serum sodium slowly rose from 128 to 135 milliequiv. per liter, and the serum potassium varied from 4.9 to 3.8 milliequiv. per liter.

Therapy consisted of a 2800-calorie diet, containing 82 gm. of protein and restricted to 10 milliequiv. of sodium daily. From December 27 through January 26 the patient took this diet and in addition received mercurial injections and calcium chloride by mouth, with a minimal diuretic response; on January 18, 5.5 liters of ascitic fluid was removed for cytologic study and because of respiratory distress. Subsequently, the tremor, which had abated, recurred to a slight degree in association with mental confusion. On January 27 the protein intake was reduced from 82 to 50 gm. daily, and the caloric intake was maintained by an increase in the carbohydrate isocalorically.

By February 2 the tremor had diminished in intensity, and by February 6 it was absent. At this time the patient was oriented and responded promptly to questioning. From

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¶We are indebted to Dr. Joseph Foley for the interpretation of the electroencephalographic records obtained in the Neurological Unit of the Boston City Hospital.

February 6 to March 1 testosterone propionate, 25 mg. daily, was administered intramuscularly without effect on the neurologic or mental status. On March 8 the protein was increased to 75 gm. daily, followed by increasing drowsiness within 2 days and confusion and a "flapping" tremor within 4 days. On March 12 the protein was again diminished to 50 gm. daily, with definite improvement within 3 days and complete reversal to the previous status in 8 days. Thereafter, further alterations in diet and course were documented by electroencephalograms (Fig. 1). On March 27 the protein was increased to 75 gm. daily. A definite tremor was observed 5 days later, when he was more somnolent and slow in response to questioning. Within 5 more days this progressed to confusion and disorientation. At this time (April 6) the protein intake was again decreased to 50 gm. daily, with reversal of signs within 6 days. A similar syndrome followed increases of protein to 75 gm. on April 17 and to 97 gm. on May 12, when only minimal signs were present. However, within 5 days, definite confusion and disorientation, as well as the flapping tremor, were observed. After a decrease in protein intake to 50 gm. daily on May 20, the tremor and mental signs subsided within 6 days. Thereafter, the patient was provided with the 50-gm. diet.

As noted in Figure 1 the syndrome of impending hepatic coma was produced on three separate occasions, with increments in dietary protein of only 25 to 50 gm. to the basic 50-gm. intake. A change in mood from euphoria to depression was usually the earliest abnormality in mental status observed. This frequently preceded the onset of the "flapping" tremor. On two occasions (April 6 and May 19) electroencephalograms characteristic of impending coma were obtained at times when clinically a "flapping" tremor, disorientation, depression and somnolence were observed. Several electroencephalograms (April 2, 22 and 24) showed nonspecific slow activity, usually at an early stage in the development of the syndrome. Electroencephalograms interpreted as within normal

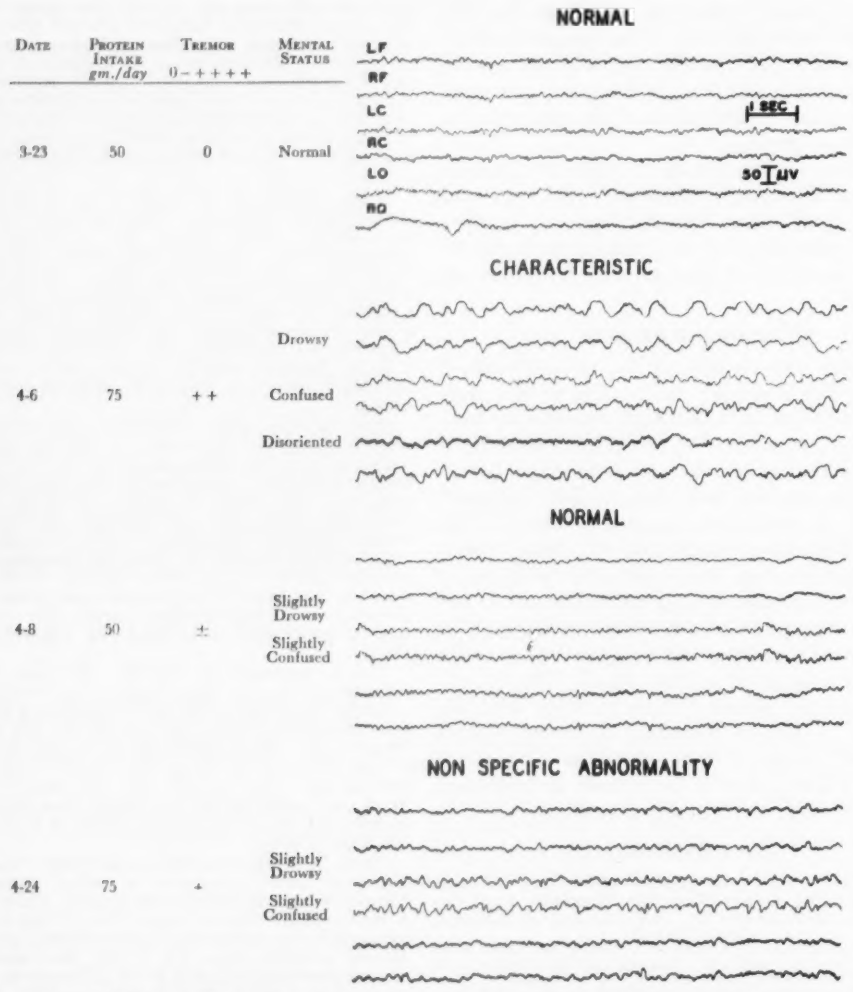

FIGURE 1. *Relation of Dietary Protein Intake, Neurologic Status and Electroencephalograms in Case 1 (See Text for Interpretation of the Electroencephalograms and the Patient's Course).*

limits were obtained on March 28, April 8 and 12, May 22 and June 2 and 5. At no time was a characteristic electroencephalographic pattern obtained without coincident changes in neurologic status. The clinical reaction and the electroencephalographic abnormalities were indistinguishable from the early stages of spontaneous hepatic coma and similar to the syndrome produced in patients with cirrhosis of the liver given "certain nitrogenous substances."[4]

CASE 2. J.H., a 42-year-old woman with chronic alcoholism, was admitted to the Boston City Hospital on February 17, 1952, because of abdominal swelling of several months' duration. On several previous admissions she had shown jaundice and ascites, and required paracenteses. On admission she had jaundice, spider angiomas, engorged abdominal veins, moderate ascites and slight ankle edema. The total serum bilirubin was 22 mg. per 100 cc., and cephalin flocculation +++. No "flapping" tremor or other neurologic abnormalities were observed. She was given daily infusions of 1500 cc. of 10 per cent glucose in water, vitamin supplements and a regular hospital diet. The quantities of food ingested could not be determined. On February 22 signs of impending coma with minimal flapping tremor were first observed, progressing during the next 5 days to stupor and coma. She was seen in consultation on February 27, when she was semicomatose and unresponsive to vocal but responsive to painful stimuli. Generalized flaccidity was noted. The course for the subsequent 5 days is given in Figure 2. Because the serum sodium concentration was 108 milliequiv. per liter, 750 cc. of 5 per cent sodium chloride solution was given intravenously, with some decrease in the depth of coma. In addition, in the subsequent 18 hours, the patient received a thick gruel providing 1500 calories, 125 gm. of glucose and 300 gm. of a proprietary low-sodium product, containing 200 gm. of milk protein and 5 gm. of potassium chloride (the serum potassium had been 2.5 milliequiv. per liter). Deep coma ensued in a few hours. The serum sodium concentration was 120 milliequiv. per liter, and the "ammonia" 7.5 microgm. of nitrogen per cubic centimeter of whole blood. Intravenous injections of hypertonic sodium chloride and multivitamins were given, and fluid intake was restricted thereafter. During the next 24 to 36 hours the depth of coma significantly decreased. The patient responded to vocal and tactile stimuli, and a coarse "flapping" tremor was elicited. Hypertonic glucose with added potassium chloride was given by stomach tube. After this, watery diarrhea occurred. During this period her mental status improved, although dehydration (the serum sodium was 151.8 milliequiv. per liter) ensued. She received a small amount of dietary protein on the 3d day and 45 gm. on the 4th day as an eggnog, in addition to parenteral administration of fluids. Elevation of temperature and deep coma preceded death.

Autopsy showed alcoholic cirrhosis, with acute hepatitis, ascites, jaundice, bile nephrosis, congestive splenomegaly, bilateral hydrothorax and hepatic encephalopathy.

CASE 3. T.H., a 42-year-old man with chronic alcoholism, was admitted to the Boston City Hospital on March 14, 1953, after 1 month of progressive jaundice, dark urine, ascites and anorexia. He admitted to 4 previous episodes of icterus, related to periods in which he had drunk large amounts of beer. On admission he had jaundice, spider angiomas, an enlarged liver, moderate ascites and peripheral edema. He was lethargic and slow in response to questioning, with a tremor of both hands. The vital signs were normal. The icteric index was 85 units. The urine gave a +++ test for albumin and a ++++ test for bile, and urinary urobilinogen was present in a dilution of 1:256. Cephalin flocculation was ++++; the alkaline phosphatase was 6.8 Bodanski units, and the blood urea nitrogen 8 mg. per 100 cc.

The patient was provided with a sodium-restricted diet, including fruit juice and 2 quarts of a low-sodium milk* and vitamin supplements daily. The mental status improved during the next 48 to 72 hours. However, because of a poor food intake, the milk was increased to 4 liters daily for 2 days, with no significant change in clinical status. Thereafter, the sodium-restricted diet and 1 liter of milk were given daily in addition to vitamins. During these 6 days he also received a mercurial diuretic, without effect. On March 24 a dose or two of ammonium chloride (4 gm. each) were given orally. Confusion, disorientation and a coarse "flapping" tremor of all skeletal muscles were observed within the next 24 hours. He was seen in consultation

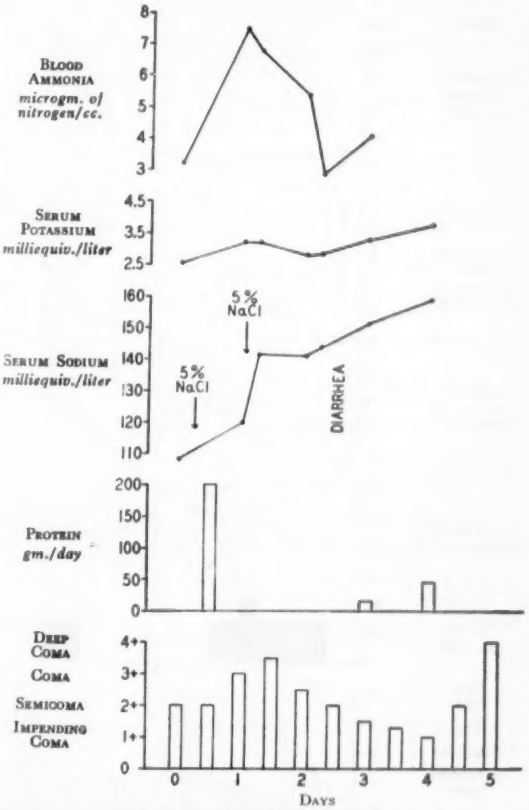

FIGURE 2. *Relation of Depth of Coma to Protein Intake, Serum Sodium and Potassium, and to Blood Ammonia Level in Case 2 (Normal Blood Ammonia, 1 to 3 Microgm. of Nitrogen per Cubic Centimeter).*

at this time. Further clinical and biochemical observations are recorded in Figure 3.

Fruit juice, sugar and 1 liter of low-sodium milk were administered daily for 8 days except for the 5th day, when he received 1.5 liters of milk. In addition 1500 cc. of 15 per cent dextrose was given daily, intravenously, for the 2d 4 days of this period. Deep coma ensued thereafter at a time when the serum sodium concentration was 117 milliequiv. and the serum potassium 3.1 milliequiv. per liter. He was given 500 cc. of 5 per cent sodium chloride intravenously but nothing else for the subsequent 48 hours. After 24 to 36 hours the depth of coma decreased, and he returned from a state of deep coma to one of impending coma. At this time the serum sodium concentration was 126 milliequiv. per liter. For the next 5 days no protein was given. A total of 2000 calories daily was provided as hypertonic glucose (1500 cc. of 15 per cent solution parenterally) and an oral fat emulsion.† Diarrhea, which was first noted

*Lonalac, available from Mead Johnson and Company, Evansville, Indiana.

†Ediol, available from Schenley Laboratories, Incorporated, Lawrenceburg, Indiana.

with the onset of impending coma, varied in intensity throughout the hospital course but was increased during the period of oral fat administration. During this time the patient was responsive, mildly confused, but alert and showed the coarse "flapping" tremor. After a 5-day period, during which his clinical status varied minimally at the stage of impending coma, an electroencephalogram showed diffuse slow-wave activity; 35 gm. of protein was given by mouth daily as low-sodium milk for 2½ days. On the morning of the 3d day he was semicomatose, and in the next 2 days he progressed to deep coma and death. Further hypertonic sodium chloride solution and protein withdrawal had no observable effect on the terminal course.

Histologic examination of the liver showed extensive fibrosis, with no acute changes.

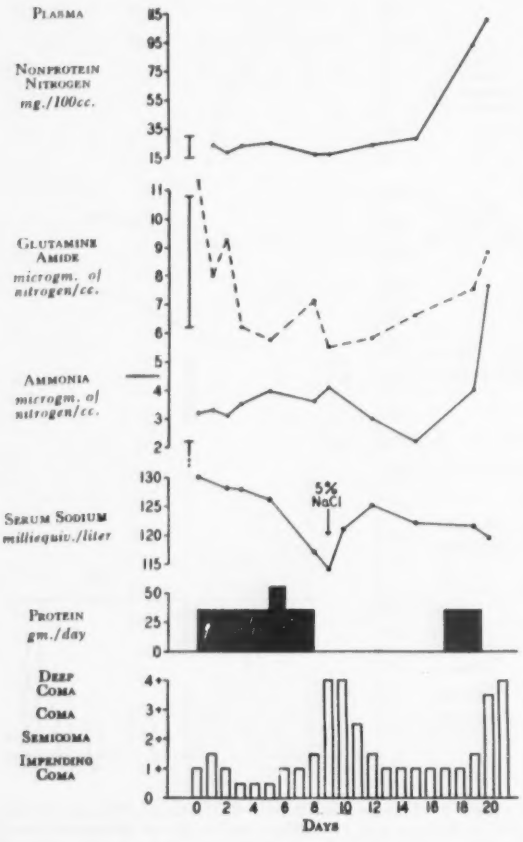

Figure 3. *Relation of Depth of Coma to Protein Intake, Serum Sodium, Plasma Nonprotein Nitrogen, Glutamine and Ammonia in Case 3.*

Vertical lines at the left of the chart give normal ranges for the plasma nitrogen fractions indicated.

During the twenty-day period of observation the serum bilirubin rose from 19.5 to 29.2 mg. per 100 cc. The serum potassium concentration varied from 3.1 to 2.9 milliequiv. per liter. The variation in other measured blood constituents is shown in Figure 3. No consistent alteration in the components of the blood or plasma was observed, although a suggestive correlation of the clinical course with plasma "ammonia" was evident.

Discussion

The cases reported above substantiate the hypothesis that an individual intolerance to dietary protein exists in patients with cirrhosis of the liver and that exceeding this tolerance may induce or aggravate hepatic coma. In Case 1 on three occasions, documented twice with electroencephalographic studies, a clinical syndrome indistinguishable from spontaneous impending hepatic coma was produced by the addition of only 25 gm. of dietary protein daily, even though the daily protein intake at this time was only 75 gm. and the diet included 2800 calories a day. The relation of the neurologic status to the administration of dietary protein is not so evident in Cases 2 and 3 since hyponatremia was a complicating factor. The observation of hyponatremia after paracentesis in patients with cirrhosis and ascites suggests that abnormalities in serum sodium concentration may have some effect on the mental symptoms observed in some patients.[9] That hyponatremia was not primarily the etiologic factor is suggested by the clinical courses of each of these patients during which the serum sodium concentration varied significantly without relation to the subsequent neurologic course.

The mechanism of this protein intolerance remains obscure. A relation to ammonia metabolism seems to exist, however. Normal tissue metabolic reactions of deamination of the amino acids of ingested proteins and bacterial enzyme action on the intestinal contents provide a continuous source of ammonia. Severe hepatic cellular damage may result in a diminished ability to clear ammonia. An alternate hypothesis, in the presence of an extensive portal collateral circulation, is that portal blood containing ammonia originating in the intestinal tract by-passes the liver.[10] In either event an elevation of blood "ammonia" or related substances to which the brain is sensitive may occur. This is suggested further by the responsiveness of some patients with cirrhosis of the liver to certain nitrogenous substances, including ammonium salts, as manifested by the production of a syndrome resembling impending hepatic coma.[4] In addition elevated blood ammonia values have previously been reported in patients with cirrhosis of the liver,[10] as well as in patients with hepatic coma.[5,6] That an altered portal circulation may be important is evident from the intolerance of Eck-fistula dogs to dietary protein. This so-called "meat intoxication" has been related to intestinal ammonia production and to the blood ammonia content.[11] The syndrome of impending hepatic coma has also been produced recently in an Eck-fistula man with a normal liver, after administration of protein and other nitrogenous substances.[12]

Previous therapeutic regimens for severe liver disease and hepatic coma have emphasized a high-protein (140 gm. daily) as well as high-carbohydrate intake,[1,13] the latter especially when deep coma was present. Patek and his associates[1] report observations similar to those of Snell and Butt,[14] who noted re-

covery from cholemia (hepatic coma) in some patients given infusions of dextrose supplemented with large doses of thiamine hydrochloride and nicotinamide. The observations reported above suggest that protein withdrawal as well as vitamin and glucose administration may have contributed to the improvement observed in these patients.

The relation of blood ammonia to dietary protein in liver disease was previously noted by Fuld.[15] He observed normal blood ammonia values in patients with cirrhosis only when the diet was poor in protein. Monguió and Krause,[11] in Thannhauser's Clinic, arrived at the following conclusions from their studies of Eck-fistula dogs:

> . . . in cases of injury to the parenchyma of the liver, preferably a diet poor in protein and rich in carbohydrates should be prescribed. A method of treatment adapted by the experienced physician intuitively, so far, has now received a definite foundation through the study discussed in the foregoing.

The therapeutic value of a nutritious diet, adequate in protein, for patients with cirrhosis of the liver is well established. The only present indication for protein restriction is the onset or presence of impending hepatic coma or coma. The daily protein intake must depend on the individual tolerance of the patient.

Summary

Three patients with severe liver disease who showed an intolerance to dietary protein are described. One patient in particular had signs of impending coma, including electroencephalographic changes, on three occasions when the dietary protein was raised from 50 gm. to 75 gm. daily; each time, protein restriction resulted in remission of the signs of impending coma and reversal of the electroencephalographic pattern to normal.

Protein withdrawal may contribute to the occasional remission of the patient with hepatic coma.

The individual tolerance for protein must be evaluated for each patient with severe liver disease and a high-protein intake avoided for patients with impending or deep coma.

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CHLORPROMAZINE IN PSYCHIATRIC ILLNESS*

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THE use of chlorpromazine (10-[3-dimethylaminopropyl]-2-chlorphenothiazine) for the treatment of psychiatric illness was started at the McLean Hospital in September, 1953. At the time of this writing it has been used in 29 cases, which form the basis of this report.

The compound is also known as largactil (Poulenc, Limited), or 4560 R.P., and as SKF 2601-A, or Thorazine.‡ It is chemically related to promethazine (Phenergan) and diethazine hydrochloride (Diparcol). It is a central-nervous-system depressant and has been applied, especially in France, to the treatment of various conditions: manic-depressive psychoses, certain schizophrenias, especially if acute and with excitement or confusion, symptoms of drug withdrawal, some psychosomatic illnesses and various conditions with vomiting. The literature on its use in psychiatry has been reviewed by Wortis[1]; the most extensive reports are those of Delay and Deniker,[2] who treated various psychiatric illnesses in France, and of Lehmann and Hanrahan,[3] who studied its effects on 71 patients in Canada.

Chlorpromazine can be administered by intramuscular injection or by mouth. In the present study the drug was prepared for intramuscular injection by dilution of the solution as supplied in a vial by the manufacturer with physiologic saline solution to which procaine was added, in the proportion of 4 drops of 2 per cent procaine solution to each 10 cc.; 50 mg. was diluted to 10 cc., and other amounts were diluted in the same proportion. The material was then injected slowly into the upper outer quadrant of the

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‡Available from Smith, Kline and French Laboratories, Philadelphia.

buttocks, two or three minutes being required for injection, after which the area was massaged for four minutes. It was found that, without the diluent, the acidity of the original solution sometimes caused painful indurations of the buttocks.

No rigid treatment schedule was maintained, but a typical schedule was as follows: 50 mg. given intramuscularly three times a day for ten days, followed by 50 mg. by mouth three times a day for five more days and, finally, by 25 mg. also by mouth, three times a day for three more days. The route and manner of administration and dosage were varied according to individual needs. If 50 mg., given intramuscularly three times a day, was insufficient after two or three days the dosage was increased to 75 mg., with reduction when improvement occurred. If improvement was slow or if the patient tended to relapse on reduced dosages, intramuscular administration or higher dosages by mouth were continued for a longer time. The drug was discontinued if marked depressive symptoms appeared. If no significant improvement occurred within about two weeks the drug was generally discontinued; usually, the effect on the course of the disease was discernible within three days — often within twenty-four hours.

For a gradually increasing rather than immediate effect, low dosages of 10 or 25 mg. by mouth three times a day were used initially and gradually increased. This method was useful in testing the reaction of disturbed senile and arteriosclerotic patients to the drug.

If possible the patient was kept in bed during the period of intramuscular therapy, to avoid orthostatic hypotension and increased drowsiness, especially during the first three days of treatment. Drowsiness, slurred speech and drooping of eyelids, which most often developed during the second day, were usually transient; if they were severe the dosage was reduced. Extreme prostration was an indication for interruption of the treatment. Blood pressure, pulse and temperature were measured at least twice a day as long as the patient was on treatment — either intramuscular or oral — since transient hypothermia and hypotension have been known to occur even late during treatment. The patient was also observed for jaundice and skin rash, although these were rare complications.

The results in various psychiatric illnesses are shown in Table 1.

Case Reports

Good Results

Case 1. A 30-year-old woman was admitted to the hospital on December 28, 1953, with a diagnosis of schizoaffective psychosis. She had had a previous mental illness at the age of 23 manifested by depressive and paranoid symptoms; this was followed by good mental health until December 14, 1953, when she stopped work, could not sleep and appeared to believe that she was going to die. She became violent and was hospitalized.

Physical examination and a roentgenogram of the chest showed compensated rheumatic heart disease with aortic insufficiency, mitral stenosis and probably mitral insufficiency. She was excited, given to tearing off her clothes and untidy, and she talked loudly and obscenely.

Chlorpromazine, 50 mg. intramuscularly 3 times a day, was started on December 31, with little immediate change. On January 2, 1954, the dosage was gradually reduced, and administration was changed to the oral route; the drug finally was stopped on January 24. By January 15 she had become much better, although her condition was somewhat variable for a few days; symptomatic recovery then apparently became complete. She was discharged on January 27. She continued to be well outside the hospital, according to the latest information (received on July 5, 1954).

Case 2. A 47-year-old woman was admitted to the hospital on May 15, 1953, with a diagnosis of manic psychosis. Premonitory depressive and hypomanic symptoms had appeared during the summer of 1952. Acutely disturbed behavior suddenly occurred on May 5, 1953, and the patient was hospitalized. She tore off her clothes and was incoherent, sleepless and constantly pacing and thrashing about. Forty-eight electric shocks were given between May 15 and September 28, with relapses within 5 days each time electric-shock therapy was discontinued; several of these relapses necessitated her return to the disturbed hall.

Table 1. *Results of Chlorpromazine in Various Psychiatric Conditions.*

Diagnosis	Good Result no. of cases	Fair Result no. of cases	Poor Result no. of cases
Manic psychoses & acute schizoaffective psychoses, with manic features	6	3	3
Acute confusional schizophrenia	1		
Excited chronic schizophrenia		3	3
Depressions		2	5
Anxiety state	1		
Senile & arteriosclerotic psychoses		2	

Intramuscular administration of chlorpromazine, 50 mg. 3 times a day, was started on October 2. By October 7 she had become quieter but was still incoherent in speech and seemed slightly drowsy. She was co-operative and rational in speech by October 9. Therapy was discontinued temporarily on October 13 because of indurations at the site of injections. Between October 16 and October 19 the drug was given intramuscularly in doses of 25 mg. 3 times a day. Improvement continued until discharge on November 4. After discharge she continued to be in satisfactory health, but with mild mood swings, last information being received on July 7, 1954.

Case 3. A 38-year-old woman was admitted to the hospital on August 30, 1953, with a diagnosis of schizoaffective psychosis. During that month she had gradually become increasingly concerned about various matters. On August 28 she started talking constantly and was sarcastic, illogical and sleepless. Between September 3 and October 13 she was given 22 electric shocks, with no improvement. In addition insulin, started on an ambulatory basis before electric-shock therapy was stopped, produced no benefit.

Intramuscular injection of chlorpromazine, 50 mg. 3 times a day, was begun on October 14. The patient became drowsy 2 days later, and the dosage was reduced to 25 mg. given intramuscularly 3 times a day. By October 17 she was less drowsy and also much improved. The drug was stopped on October 26, and improvement continued to complete recovery. She was discharged on October 30. After discharge she continued to be well, resuming household duties and care of children. Last information about her was received on July 8, 1954.

Case 4. A 38-year-old woman was admitted to the hos-

pital on June 4, 1953, with a diagnosis of schizoaffective psychosis. Four episodes of similar mental illness had occurred in 1937, 1945, 1949 and 1951, 2 to 5 months in duration, and had been treated variously by insulin shock, insulin administration and electric shock. The electric shock had had an adverse effect. The present illness had started in June, 1953, when the patient became overactive, sarcastic and somewhat deluded, believing that her children might be kidnaped.

Examination showed an overactive, sarcastic, somewhat deluded and disintegrated behavior pattern. There was no improvement in the hospital before electric shock; 4 treatments given between August 21 and September 1 caused slight improvement, but the treatments were stopped because of objections of the patient and family. Intramuscular administration of chlorpromazine, 50 mg. 3 times a day, was started on September 16. She was drowsy on the next day the first showed distinct improvement on September 18. The drug was stopped on September 19, but improvement continued up to the time of discharge on September 24. Information received on July 7, 1954, indicated that she had remained as well as was usual for her between illnesses.

CASE 5. A 55-year-old woman entered the hospital on March 11, 1954, with a diagnosis of manic psychosis. For about 1 year she had shown slowly increasing activity in volunteer charity work and also exhibited poor judgment, especially in money matters. During February, 1954, she began to manifest great excitement and disorganization. On March 1 she was admitted to a general hospital, where she became preoccupied with various unrealized plans, with delusional tendencies. One day she rolled about on the floor, struck out and spoke in a nearly incoherent manner.

On admission chlorpromazine, 50 mg. intramuscularly 3 times a day, was immediately begun. On March 12 she was quieter, and on March 13 she became co-operative, sociable and attentive to her personal needs; however, she still tended to think of various plans without restraint or judgment. On April 1 the dose was changed to 50 mg. by mouth 3 times a day; later it was reduced, and finally the drug was stopped. She remained in the hospital until July, with continued gradual improvement.

CASE 6. A 17-year-old girl was admitted to the hospital on February 25, 1954, with a diagnosis of schizoaffective psychosis. Her schoolwork had become poor and her behavior to her mother rebellious during 1951 and 1952. The psychosis had started suddenly in August, 1952, lasting until January, 1953. She showed a varied clinical picture while psychotic, exhibiting changing proportions of assaultiveness, withdrawn behavior, overactivity with hilarity, erotic behavior and critical attitudes. After this she was fairly well and was given psychoanalytic therapy from March to December, 1953, while going to school. Difficulty gradually recurred in December. She was somewhat withdrawn but not grossly disturbed until April, when, in connection with impulses to act out material brought out in psychotherapy, she lost control, entered other patients' rooms without judgment and became excited and untidy.

Administration of chlorpromazine was started on April 19, 1954, in doses of 50 mg. given intramuscularly 3 times a day. On April 21 this was changed to 50 mg. by mouth and then gradually reduced. After the 1st dose the patient could sleep again; her behavior improved, and psychotherapy could be continued. The dose was reduced, and the drug was stopped during May, with an increase in symptoms but with continuance of psychotherapy. Up to July, 1954, the symptoms were varied, but slow progress was being made.

CASE 7. A 20-year-old girl was admitted to the hospital on November 7, 1953, with a diagnosis of schizoaffective psychosis, with blocking and confusion. She had begun to show gradually increasing concern about her social abilities and had postponed her impending marriage. Five days before admission she had become fearful, depressed and nearly mute.

During late November she was treated with insulin therapy on an ambulatory basis, with no improvement. Four electric-shock treatments were given early in December, with improvement followed by somewhat hypomanic behavior, and then relapse into muteness. Eleven additional shock treatments were given between December 31, 1953, and January 25, 1954. Relapse was again evident by February 3. Intramuscular administration of chlorpromazine, 50 mg. 3 times a day, was started on February 12. The drug was stopped 4 days later because of hypothermia and labored breathing. It was begun again on February 17 in doses of 50 mg. by mouth 3 times a day. By February 18 she showed distinct improvement. Thereafter the dose was gradually reduced, and the drug was finally stopped on March 9. The improvement continued to complete recovery on discharge on March 26. She continued to be well outside the hospital, according to information received on July 8, 1954.

CASE 8. A 49-year-old woman entered the hospital on December 11, 1953, with a diagnosis of anxiety state. A previous illness in 1937 had lasted 6 months and had been diagnosed as manic-depressive psychosis with paranoid tendencies. Thereafter she was well until early December, 1953, when she became anxious and depressed in the midst of a perplexing social situation.

On admission she was very tense, restless, depressed and uncertain, with fears of impending catastrophe. Intramuscular administration of chlorpromazine was started on December 17, in doses of 50 mg. 3 times a day. She became drowsy for a short period on December 19. She was much less tense by December 21, and improvement continued thereafter. The dose was reduced, and the drug later stopped. She was discharged on January 4, much improved. During further convalescence outside the hospital she continued to improve, no further information being received after January 15, 1954.

Fair Result

CASE 9. A 27-year-old woman was admitted to the hospital on March 26, 1953, with a diagnosis of paranoid schizophrenia. Symptoms of depression, withdrawal and hostility had begun at the age of 18. By the age of 25 the patient had become hallucinated.

On admission she was argumentative, unsociable, disdainful of those she considered inferior to her and preoccupied with the significance of her phantasies and ideas. She soon became demanding and unreasonable and was not amenable to explanations; she was occasionally violent and threatening, having phantasies of killing. Electric-shock therapy and insulin therapy on an ambulatory basis were given, with poor results; neither of these was employed during the 3 months before treatment with chlorpromazine.

Intramuscular administration of chlorpromazine, 50 mg. 3 times a day, was started on September 24. No drowsiness occurred, and improvement was noted within 3 days. The dose was reduced gradually, and the drug was finally stopped on February 4, 1954. Administration was accompanied by better sociability, relaxation and ability to participate in hospital activities, but there was no essential change in quality of thinking. Irritability and unreasonable behavior again appeared at the time chlorpromazine was discontinued and kept increasing until the drug was again started on April 12 in doses of 50 mg. by mouth 4 times a day. By April 14 the patient was quieter and less demanding and enjoyed a few activities. She then appeared pleasant to those about her, although she continued to make occasional unreasonable requests. Use of the drug until July, 1954, was accompanied by continued response as described above.

Effect in Depression

CASE 10. A 54-year-old man entered the hospital on November 25, 1953, with a diagnosis of psychoneurotic depressive reaction. During the previous summer the obsessive (and mistaken) idea that his wife might be pregnant developed, and he continued to worry. On admission he was agitated and depressed.

Chlorpromazine administration, 50 mg. intramuscularly 3 times a day, was started on December 1. This was later reduced, and the drug was stopped on December 15. During the treatment he was less distractible, slept better and showed some lethargy, but he continued to be depressed and to wonder whether his wife was pregnant. After chlorpromazine was discontinued, electric-shock therapy was begun, and improvement resulted.

Fair Result

CASE 11. A 75-year-old woman was admitted to the hospital on March 6, 1954, with a diagnosis of senile psychosis. Two or 3 years previously she had begun to experience difficulty in remembering names and events and had become confused in conversations. On admission she was very confused and variable in behavior, often being quiet during the day but showing marked disturbance and untidiness, with smearing of feces, at night. She was given a mixture containing Metrazol and nicotinic acid and became more excited. Chlorpromazine therapy, in doses of 25 mg. 4 times a day, was started on April 8. On this regimen her combativeness stopped, and she became somewhat quieter, slept better and no longer smeared feces. She retained this improvement until discharge on May 4.

DISCUSSION

Experience with 29 cases makes it evident that chlorpromazine is capable of strongly influencing the course of some psychiatric illnesses. Although much additional experience will be needed to establish its place in the treatment of the various types of psychoses, present evidence suggests that its greatest value is for patients with acute symptoms of increased psychomotor activity, regardless of whether this occurs as a manifestation of manic or acute schizoaffective psychosis. In these forms of illness the drug appears to compare favorably with electric shock as a therapeutic agent and, indeed, seems to have certain advantages. The therapy is comparatively free of the phenomenon of sudden relapse after discontinuation of treatment, which often occurs with electric shock. Chlorpromazine is also comparatively free from troublesome complications, and can be given to patients whose physical illness precludes the use of electric-shock therapy. It can be administered almost immediately after admission, without extensive examinations, and its effect can be estimated within two or three days. It can, of course, be replaced by other somatic therapy if no improvement results. A unique advantage over electric-shock therapy for psychiatrists interested in following patients in psychotherapy is the lack of memory loss and of sudden changes in mental content.

Although chlorpromazine may cause the patient to appear very drowsy and to allow sleep at night, it does not seem to produce marked somnolence or markedly to reduce intellectual capacities or alertness. Its use is not accompanied by disinhibition, — the release of emotions and thoughts previously held in check, — a phenomenon often observed when barbiturates or other sedatives are given.

It is to be noted that 3 of the recoveries reported above occurred in patients who were resistant to electric shock. However, it is possible that the recovery that followed the administration of chlorpromazine was actually related to the fact that electric shock had previously been given. The relation between the effects of electric shock and those of chlorpromazine should be given further study. Experience in Case 7 confirms earlier reports of benefit in acute confusional schizophrenias by Delay and Deniker.[2] The drug may prove to be useful in other acute schizophrenias in which depression is not an outstanding component.

Chlorpromazine may have some effect on the agitation or excitement of chronic schizophrenia; it appears to induce calm without changing mental content significantly. Patients so preoccupied with special ideas or delusions that other activity is precluded may relax and may be able to divert their interest to other things. The drug does not appear to diminish hallucinosis.

There is little experience with the use of chlorpromazine in agitated senile or arteriosclerotic patients, but observations made so far indicate that mild calming of overactivity and increased ability to sleep may result.

Depressions notably do not respond well. If mixed elements of depression and increased psychomotor activity are present, the drug should be used cautiously and should be stopped when there is any suggestion of a great increase in depressive symptoms.

Chlorpromazine has not been extensively employed in anxiety states and other psychoneuroses at McLean Hospital. Although this type of study has been made by others, the subject needs further exploration.

The drug probably should not be given intramuscularly or in high oral dosages to outpatients, except those under constant nursing supervision, because of the possibilities of prostration, hypotension and extreme drowsiness. Further experience may clarify its possible use in certain outpatients.

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COLONIC SYMPTOMS WITH ACTIVE DUODENAL ULCER

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THE case reported below and similar experiences have made it increasingly clear that recurrent symptoms of an irritable colon are sometimes the principal or only clinical evidence of active duodenal ulcer. This observation led to a study of the frequency and importance of this phenomenon.

In October, 1946, A.S., a 44-year-old tool-and-die worker, was seen at the Hartford Hospital because of severe abdominal distress over the cecum and along the descending colon. In April of the same year he had been studied because of pain in the epigastrium, with radiation down the left side of the abdomen. A gastrointestinal series had revealed an incisura in the duodenal cap and a possible ulcer crater. With a 6-feeding diet, belladonna, aluminum hydroxide, amino acids and mineral oil his symptoms subsided, but in August, 1946, his bowel movements became painful, he stopped the mineral oil, and his abdominal pain returned. This distress, which was crampy and colicky, occurred in waves shortly after eating and was relieved by the passage of flatus. On re-examination in October, the duodenal cap ballooned out normally, with no evidence of ulcer or deformity. A consultation note at that time concluded as follows: "In my opinion the present problem is relief of colonic spasm, reassurance of a somewhat rigid and difficult personality, and prevention of recurrence of peptic ulcer, which is known to have been present in the past."

The patient was readmitted to the hospital in November because of persistence of the same distress. Another consultant stated that the symptoms were "inconsistent with duodenal ulcer as I know it." At that time an exploratory operation was performed, during which the surgeon noted the deformed duodenal cap.

In March, 1947, a subtotal gastrectomy was carried out. After that there was a complete and permanent remission of symptoms. In 1953 a circumcision was performed. At that time the patient's interval digestive history was entirely normal.

TABLE 1. *Colonic Symptoms in 269 Patients with Duodenal Ulcer.*

SYMPTOM		NO. OF CASES
Colonic malfunction (any type)		108 (40%)
Constipation	98 (36%)	
Diarrhea	5 (2%)	
Alternating constipation & diarrhea	5 (2%)	
Mucoid stools	3 (1%)	
Pain in lower abdomen	40 (15%)	
Small or hard stools	26 (9%)	
Gas or bloating	18 (6%)	
Irritable colon		47 (17%)
Two or more colonic symptoms, including pain in lower abdomen or diarrhea		

MATERIAL, METHODS AND OBSERVATIONS

The detailed medical histories of 269 patients with duodenal ulcer were recorded in a medical office. These were analyzed in an effort to determine the frequency of colonic disturbances and frank symptoms of irritable colon in patients with active duodenal ulcer (Table 1). The first subhead of this table lists all patients with any colonic disturbance such as constipation, diarrhea, alternating constipation and diarrhea, small, hard stools, mucoid stools, pain in the lower abdomen, gas or "bloating." The second subhead concerns cases in which a diagnosis of irritable colon could be justified on the basis of pain in the lower abdomen or diarrhea and at least one additional colonic symptom. From this table it is apparent that 40 per cent of patients with active duodenal ulcer have some kind of colonic malfunction and that 17 per cent have frank symptoms of irritable colon.

TABLE 2. *Symptoms of Colonic Malfunction in 269 Patients with Duodenal Ulcer.*

EVIDENCE OF COLONIC MALFUNCTION	NO. OF CASES
Colonic symptoms	108 (40%)
Colonic symptoms only during exacerbations	83 (31%)
Colonic symptoms during & after exacerbations	13 (5%)
Coincidental colonic symptoms (before, during & after exacerbations)	12 (4.5%)

The data were also analyzed to ascertain the number of patients whose colonic symptoms appeared to be related to activity of the duodenal ulcers in contrast to those with coincidental colonic symptoms. The 108 subjects with symptoms of any sort of colonic dysfunction constituted 40 per cent of the ulcer patients under study. Of these, 83, or 31 per cent of the patients with duodenal ulcer, had colonic symptoms only during periods of ulcer activity. Another 13, or 5 per cent, had symptoms of colonic malfunction arising during exacerbations and persisting for an indefinite period thereafter. Only 12, or 4.5 per cent, had "coincidental" colonic findings that were present before the ulcer became active. These findings (Table 2) indicate that in most cases there is a definite chronologic relation between the onset of ulcer activity and the colonic malfunction that may accompany or follow it.

The observations on patients with frank symptoms of irritable colon were similarly tabulated. Although the prevalence was lower, the chronologic relations were identical. Forty-seven patients with ulcer (17 per cent) had symptoms of irritable colon. Of these, 27 (10 per cent of the entire ulcer series) had evidence of colonic irritability appearing with exacerbations of their ulcers and persisting afterward. There were only 8 (3 per cent of the series) with coincidental

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irritability of the colon that was present before the ulcer became active.

Discussion

The concept of bowel dysfunction secondary to disease of the upper gastrointestinal tract is not new.[1-5] Burton,[6] in his *Anatomy of Melancholy* (published in 1621), quotes Mercurialis as saying: "The stomach is the King of the belly, because if he be distempered, all the rest suffer with him, as being deprived of their nutriment, or fed with bad nourishment, by means of which some crudities, obstructions, wind, rumbling, griping, etc." And Bockus[7] makes the following comment:

> Symptoms depending upon colonic dysfunction occur rather frequently in association with active peptic ulcer. Obviously they have no importance diagnostically, except at times they may be sufficiently severe to mask the symptoms of ulcer, or to confuse the inexperienced historian.

Table 3. *Classic Symptoms of Irritable Colon in 269 Patients with Duodenal Ulcer.*

Symptom	No. of Cases
Total with irritable colon	47 (17%)
Irritation only during exacerbations	27 (10%)
Irritation during & after exacerbations	12 (4.5%)
Coincidental irritation (before, during & after exacerbations)	8 (3%)

The case reported above and clinical observation on many patients with similar histories indicate quite clearly that colonic symptoms at times completely overshadow the classic distress of active duodenal ulcer. However, since the colonic symptoms appear for the most part to be secondary to activity of the ulcer, they tend to be periodic. For this reason, when a patient with a deformed duodenal cap observed on x-ray studies has episodes of colonic malfunction that are separated by long asymptomatic remissions, recurrent ulcer activity should be considered probable.

The frequent occurrence of constipation in patients with active duodenal ulcer is often attributed to aluminum hydroxide or other constipating antacids. In many cases constipation may be caused or aggravated by such substances. In accumulating the data for the present study, however, we took precautions to record constipation only when it was present before antacids were administered.

No attempt has been made in this clinical study to arrive at the physiologic mechanism by which colonic malfunction occurs with ulcer activity. It is possible that the gradient of intestinal motility described by Alvarez is intensified by the inflammatory reaction around the crater in the duodenum and thus leads to abnormal spasticity in the colon. This general hypothesis receives support from the dramatic disappearance of irritable colonic symptoms that sometimes follows subtotal gastrectomy, as in the case reported above.

It is apparent from Tables 2 and 3 that the colonic disturbances that appear with active duodenal ulcer sometimes persist temporarily after the ulcer symptoms have disappeared. This phenomenon should be kept in mind to guard against disappointment on the part of a patient who is not completely relieved by his ulcer therapy.

Conclusions

Colonic disturbances are frequently noted in association with active duodenal ulcer.

Forty per cent of patients with active duodenal ulcer have some form of colonic malfunction, whereas only 4.5 per cent have malfunction of the colon before the onset of ulcer symptoms.

Seventeen per cent of patients have classic symptoms of irritable colon during ulcer activity, but only 3 per cent experience these symptoms before the onset of the exacerbation.

In 5 per cent of patients the colonic symptoms, which appear with the exacerbation, persist for a period of time thereafter.

In a small number of patients the manifestations of colonic irritability overshadow the symptoms of ulcer and lead to diagnostic confusion.

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Correction: The second paragraph of the right-hand column on page 463 of the article, "Immunization of Adults against Diphtheria and Tetanus," by Dr. Johannes Ipsen, Jr., which appeared in the September 16 issue of the *Journal*, should be supplemented as follows: The Commission on Immunization, like the other commissions of the Armed Forces Epidemiological Board, does not conduct work but sponsors it. The actual work referred to was carried out by Dr. Geoffrey Edsall and his associates, largely under a contract between Boston University School of Medicine and the Office of the Surgeon General, United States Army. A full report of this work will appear in the *American Journal of Public Health.*

SPECIAL ARTICLE

INDUSTRY'S CONTRIBUTION TO THE FUTURE OF MEDICINE*

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MEDICAL progress is of vital interest to the employed person, the physician and the community. The machine age of today is helping, rather than hindering, mankind in its search for health. Heretofore, the conflict of man and machine has been such that accident, illness and sudden death have been accepted as necessary for progress. Now, thanks to the present interest in the field of human relations in industry, leading universities are conducting research programs, supported by both labor and business, to improve the health of the worker. Top executives and experts in scientific management and medical, public and employee relations are holding frequent meetings on various phases of the subject.

The industrial health of the employed population is important if maximum utilization of the human resources of the country is to be maintained for efficient production and full employment.

Progressive management no longer confines its activities to the engineering sciences, fundamentals of sanitation and public health, lighting, temperature, ventilation and physical safety when considering industrial health. More and more interest, time and money are given to the social sciences, in which the physician's knowledge, experience and appreciation are outstanding. Nevertheless, to date, the physician has failed to impress the public at large with his unique capabilities in the field of social science.

All physicians are conscious of much unsound medical legislation, the result of great public fear when epidemics spread over the country many years ago. Today, with the general public becoming more alert to personal health needs, there is a similar public fear that, in certain circles, is causing demand for medical legislation. To offset this possibility, the ideals of the profession must be correctly and earnestly promulgated.

With the appreciation of this fact it behooves the various members of the medical profession — the internist, the surgeon, the ophthalmologist, the neuropsychiatrist, the physician in industry, and the general practitioner — to understand the meaning of teamwork and human relations. The whole fabric of any community — all the political, social and economic bonds holding its various segments together — depends on the provision of having jobs and opportunities to make a living. Human relations on the job are much more complicated than other aspects of living. At other times and places a person is left largely to his own devices, but at work he has to adjust himself not only to the job itself and its physical environment but also to his supervisors, other people around him and the rules and regulations of the organization.

There is abundant evidence that many workers are not adjusting themselves properly. Many such people are not well. Naturally, the question arises regarding the best method of determining the exact nature of their illnesses. It cannot be assumed that a person is perfectly well when he shows up for work in the morning; likewise, it cannot be taken for granted that he is ill when he stays away. Such thoughts bear directly on the question of absenteeism.

Unfortunately, perhaps, the average practicing physician confines his interest to the immediate problem of the patient. He readily detects physical defects, but time alone often prevents him from evaluating the patient's entire personality — the combination of his traits, reactions to other persons and to strain and stress, and his particular emotional make-up and pattern — in other words, his entire physical, mental and social state.

It is my conviction that medicine as an independent scientific and cultural endeavor must in future devote itself to this important constructive approach.

A popular campaign of public education is needed to persuade people, for their own good, to demand thorough periodic medical examinations. Medicine in industry, as practiced by many leading concerns, is doing much to assist the profession in the performance of this phase of its job.

To be most effective in its approach the medical department of an industrial organization is necessarily independent, the physician in charge reporting directly to top management, where he receives an immediate and just hearing. In this respect he acts in the capacity of consultant to management regarding the rapidly growing medical phase of human relations. Progressive, foresighted managements that have acknowledged this principle have been able to appoint leaders in the medical profession to their staffs.

The modern concept of an industrial medical department implies that it is a service unit — of service primarily to the employee in professional consideration of his personal well-being; to the employer who, out of interest in employee welfare, finances the enterprise; and to the public at large, which eventually benefits.

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It is reasonable to assume that, in the not-too-distant future, all problems of a medical nature having to do with the employed person will be interpreted in terms of how a particular condition affects or is affected by the employee's actual working environment. This is a far cry from considering personnel medical problems exclusively in the light of absentee records. It is a forward-looking, all-inclusive policy that has its roots in the periodic health inventory.

Periodic Health Inventory

The periodic health inventory of individual employees is obligatory for a modern corporation's constructive health-maintenance program. The program actually begins with the placement examination, which goes beyond the usual so-called pre-employment examination. Far more details are sought here; the new employee is considered in relation to his job, the physical examination per se taking its rightful place in the medical analysis of the total person.

The next step is the performance of a comprehensive periodic inventory at suitable intervals determined by the examining physician. Such an inventory will include the sociologic history of the employee, all emotional factors, his reaction to stress and strain, and the character of his home life and outside activities — all of which, when coupled with the actual physical findings, give the examining physician the facts necessary to consider the employee from the point of view of *total environment*. This is the 1954 way of saying what the general practitioner of the 1920's knew when he "saw all, heard everything" but said nothing to his patient.

Once a constructive health-maintenance program has been started and periodic health inventories of all employees have been made, the environmental approach can be carried one step farther. All employees, from a strictly medical point of view, may be placed in one of the following eight classifications: normal health; situational state (no existing disease); functional disease (existing lesion); neuropsychiatric state; cardiovascular disease; neoplastic disease, metabolic disorders; and all other medical problems. A few of these are considered at length.

Normal Health

The properly managed constructive health-maintenance program assumes that, if the patient in industry is still capable of doing an efficient job, he is normal until proved otherwise.[1]

This state may well exist even in the presence of such abnormalities as heart disease, arthritis, kidney or liver disease, hypertension or arteriosclerosis. All these are, in a high percentage of cases, physiologic changes that can be anticipated as normal age progresses. In other words these diseases may be considered the inevitable rewards to which man falls heir as he follows the natural course of aging. The important point is for the man to learn his limitations and how to live a full life within them.

A wise man once put it in more picturesque fashion: "He who fills up every hour of his life with activities within his abilities to perform will insensibly glide into old age without perceiving its arrival, and his powers, instead of being suddenly and prematurely extinguished, will gradually decline by the gentle and natural effect of accumulating years." These words of Cicero appeared in an article entitled "On Old Age" written nearly fifty years before Christ. They are as true now as they were then.

It is immediately apparent that this approach to the patient — the assumption of normalcy — is diametrically opposed to what one was taught in medical school, and to the philosophy to which the student of yesterday and the average doctor of today were exposed throughout the professional training period. I was taught to consider each patient as having some type of disease until the contrary was proved. In other words each patient, because he was a patient, and had come to the doctor, was abnormal.

No longer, as Berry,[2] of Harvard, has clearly pointed out, does one take this negative attitude. Without question, the new, positive approach is most practical when applied to industry. Eventually, it may be applied in general to medicine, which will then be in a true "era of normalcy."

Situational State

Before the situational state can be clearly understood, this must be defined. Both World War II and the Korean War offered evidence that every man has his emotional as well as physical "end point." For many reasons, among which could be listed improper job placement, unhappy home or working environment and lack of intelligent observation by a responsible supervisory staff, many persons in industry are approaching this end point. Once this point has been reached they will become the unemployables of industry. Therefore, this term is applied to the vague group of complaints affecting persons whose end point is being reached after varying periods of exposure to circumstances beyond their control and against which they are powerless to act.

The situational state, together with its more advanced form, — the functional disease, — may be detected early, provided the local superintendent, foreman or superior is alert to the situation. It can be detected early for the simple reason that the employee's work efficiency begins to suffer as his end point is approached. Therefore, theoretically, most of these employees can be handled successfully by other than medical personnel with the proviso that they are trained in *human welfare* and *understanding*. It is an accepted fact that functional illnesses, or so-called psychosomatic complaints, have their

origins in nonmedical sites and, generally speaking, occur in persons eighteen to thirty-six years of age.

Patients with the more severe situational states and the functional disorders should, of course, be referred to the doctor in industry. He is the agent most capable of diagnosing and suggesting remedies — usually by changing the worker's environment.

An employee suffering from a severe situational state could very easily progress, if not under competent observation and treatment, to the status of a person with a real functional illness showing definite organic change. The most common example in industry — perhaps the elite of all the functional illnesses — is the duodenal ulcer. The ulcer has been called the "wound stripe of civilization." It would be better, perhaps, to call it the service badge of competition, for it is in the highly competitive industry of today that the natural progression from situational to functional disease, followed by ulcer formation, is most common.

Neuropsychiatric State

The situational state, if unchecked in its early stages, can also progress normally to the fourth classification — that of the neuropsychiatric conditions. These patients often slide rapidly into full-blown neuroses, manifested by anxiety states, severe depressions with suicidal tendencies, or conditions of complete withdrawal bordering on the psychotic.

A common evil halfway between the situational state and actual neuropsychiatric disease is alcoholism. Too often, problem drinking[3,4] has its roots in a combination of situational difficulties and emotional factors that, if detected early enough, would have prevented the development of the sodden, half-man who haunts the offices of personnel directors and physicians both within and outside industry. Although the concept of problem drinking as a disease and the consideration of the factors that lead a man to become an alcoholic are currently regarded as new, the following description was written by Charles Lamb, in his *Confessions of a Drunkard*, in 1822:

> Twelve years ago I was possessed of a healthy frame of mind and body. I scarcely knew what it was to ail anything. Now, except when I am losing myself in a sea of drink, I am never free from those uneasy sensations in head and stomach which are so much worse to bear than any definite aches and pains.

Other Conditions

In the remaining classifications — cardiovascular, neoplastic, metabolic and others — the physician in industry is often the one to make the diagnosis. Once this has been done, he refers the patient to physicians outside the company for definite therapy. He remains in the picture only as the member of the team who made the diagnosis. Of course, he continues to act as liaison man between the patient and his private physician on the one hand and the company on the other.

All disease — whether it is neuropsychiatric, cardiovascular, neoplastic, metabolic or other — is more easily cured if it is detected early. Early detection is the watchword of the physician in industry. It is only by early detection, followed by correct *supervised* therapy that the employee will be returned to the classification into which all employees fall in an ideal industrial medical setup — namely, normal health and adjustment.

Discussion

The modern corporation, if guided by competent medical service, is on solid ground as far as public opinion of its attitude toward its employees is concerned. The employee, in turn, profits by this managerial interest in his behalf. He feels better, has more energy and performs his duties in a manner that is beneficial to him and to his family as well as to his employer. Assignments with such progressive companies are a challenge to the qualified physician. He is in a position to do so much for so many.

To maintain health "requires the ingenuity of many, the application of the accepted knowledge of the few, and the appreciation of its worth to employer and employee alike."[5] Unfortunately, most employers still think of health in its negative sense—in terms of drugs and hospitals, pain and worry, sickness and death. Yet they should be thinking of health in terms of mental and physical vigor and the ability of a worker to enjoy a useful and productive life with his fellow associates. Enlightened employers realize the importance of this positive approach to the question of health. They measure the health of an industrial worker with statistics on housing, nutrition, production and employment rather than with statistics on absenteeism, frequency of accidents, morbidity and mortality.

The tools of constructive medicine[6] are many. Knowledge of normal human physiology and the physiologic aspects of disease is only one basis for improving health, for there are others: better nutrition, guidance in selection of occupation, avoidance of prolonged and excessive fatigue, proper balance between work and play, selection of appropriate physical exercise and general habits compatible with physical and mental well-being.

Such a program requires a complete understanding of purpose among the patient (when he is well and when he is ill), the employer and his physician. Teamwork within the medical profession is the next prerequisite. The physician in industry, the general practitioner and the consultant must consider the entire problem in terms of the patient if they are to justify the ideals of the profession.

Industry's growing interest in the field of human relations affords the competent physician an opportunity to practice medicine in its broadest sense. He acts as a medical consultant to the worker, to the

employer and to the private physician. He renders an unbiased and effective service to all.

Thanks to industry, the average employee is now getting better medical care than he ever got before. Because he is healthier he produces more. In turn, industry is able to provide more effective medical care in steadily increasing quality. Here, then, is a reward that both labor and management are enjoying together.

I subscribe to the theory that the health problems of competitive enterprise are not complex, assuming, of course, that management and the medical profession acknowledge the over-all problem and are willing to do something constructive about it. The present-day "curative" approach to the health needs of the nation, in terms of cost and often questionable proficiency, is staggering both in scope and in effect. On the other hand, the positive route, with its potential value in the realm of good human relations, is still underdeveloped territory. A healthy, happy and suitably occupied person is a good citizen.

Conclusion

A fitting conclusion to these remarks is given by the following words of Lemuel Shattuck, written a hundred and four years ago:

> The science of preserving health and preventing disease should be taught as one of the most important sciences. It would be useful to all, and particularly to the student of curative medicine.

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MEDICAL PROGRESS

DIABETES MELLITUS

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IN this report, the following aspects of diabetes mellitus are considered: biochemistry and physiology; pathology and pathogenesis; diagnosis; associated conditions; treatment; pregnancy and diabetes; and complications.

Carbohydrate Metabolism

The experimental use of C^{14}-labeled molecules continues to expand knowledge of the role of insulin in accelerating carbohydrate metabolism. In general the acceleration takes place at two widely divergent points: at the introduction of glucose into the glycolytic cycle and at the entrance to the tricarboxylic acid cycle. The latter is the junction of reactions in equilibrium with protein and fat metabolism on the one hand and oxidation to carbon dioxide on the other. The details are still the subject of investigation.

Regarding the first point, it is not yet settled whether insulin acts by accelerating the hexokinase reaction directly or through an effect on its sources of energy phosphate or, more probably, by facilitating the transfer of glucose across the cell membrane. Recent quantitative estimates of "energy phosphate" (adenosinetri-and diphosphate and glucose-1-phosphate) in livers of normal and alloxan-diabetic animals did not reveal a decrease commensurate with the metabolic defect.[1] Moreover, studies under anaerobic conditions demonstrate that the diaphragm of the normal rat continues to utilize glucose in the presence of insulin at a normal rate even though adenosinetriphosphate (ATP) concentration continues to fall to very low levels.[2] Thus, the action of insulin seems to be independent of ATP.

It has been suggested that insulin introduces glucose into the glycolytic cycle not by any action on hexokinase phosphorylation but by transferring this sugar across the cell membrane. This action is most clearly demonstrable by study of the accelerating effect of insulin on the partition between the extracellular and intracellular spaces of sugars whose transfer is accelerated but that may or may not be subsequently utilized. These studies were performed on such varied sugars as C^{14}-labeled fructose, mannose, sorbitol, galactose, arabinose and xylose in pancreatectomized and eviscerated animals, and in vitro on rat diaphragm.[3-7] Some of the sugars remained in the extracellular compartment, and others penetrated the cell membrane but were not utilized. The penetration of monosaccharides into the aqueous humor of the rabbit's eye has also been confirmed.[8] The nature of the chemical reaction accelerated by insulin and responsible for such transfer of sugars is not clear, but there is some evidence that it is related to the chemical configuration of the terminal three-carbon atoms of the sugars. By study of the transfer of two sugars, glucose and galactose, competition could be demonstrated between them, as if for a place in a quantitatively limited reaction.[6] Finally, it was

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shown in vivo that muscular activity could accelerate the transfer of the same sugars as insulin did — and probably by a humoral mechanism since the muscle was isolated neurologically. This seems to be a fruitful approach to the exact locus of insulin action at the onset of glucose metabolism.

In the eviscerated rabbit supplied with adequate insulin the oxidation but not the disappearance rate of glucose is strikingly and immediately depressed by the addition of either betahydroxybutyric acid or acetate.[9,10] This preferential displacement of glucose even in the face of intense insulin action implies that insulin is less effective as an oxidative enzyme, and gives further support to the view held by some that its principal action may be the transfer of glucose into the cell.

The only common feature of the other reactions believed to be accelerated by insulin is their general location. In liver slices from diabetic animals insulin accelerates lipogenesis from lactate[11] a hundredfold, with an accompanying reciprocal shift from oxidation. In a more detailed study of the metabolism of the normal and diabetic rat diaphragm immersed in both glucose and pyruvate, insulin can be shown to hasten both the conversion of glucose to pyruvate and the utilization of pyruvate.[12] Finally, still in the same general area, diabetic tissues show added blocks in lipogenesis from acetoacetic acid[13] and in protein synthesis from glycine and phenylalanine.[14] It is not yet proved whether insulin accelerates these more distant pathways of carbohydrate metabolism directly or only as a secondary effect.

Protein Metabolism

In the last Medical Progress report on diabetes mellitus[15] the importance of insulin in accelerating lipogenesis was stressed. In the present report it will be shown to assume a remarkably similar role in protein metabolism. The diabetic metabolic defect responsible for nitrogen loss stems mainly from a block in protein synthesis rather than increased catabolism. This fact has been demonstrated both in vivo and in vitro as a threefold to sevenfold decrease in the incorporation of C^{14}-tagged d-l-alanine, phenylalanine and glycine into peptide (glutathione) and protein.[14,16] Moreover, in vitro, by adjustment of the experimental conditions, this was shown to be a block in synthesis rather than an accelerated breakdown.[14] This observation was further confirmed by comparison of the disappearance rate of S^{35}-labeled (methionine) serum protein injected into normal and diabetic dogs.[17] There was no difference between the two. The rise in the hepatic concentration of succinic dehydrogenase and aspartic-glutamic transaminase in diabetes[18] is not necessarily evidence for excess catabolism, since the increased concentration might be expected to be true for enzymes useful in the disposal of amino acids regardless of the cause of the excess accumulation of the acids. This illustrates another specific reaction accelerated as a result of insulin action.

Protein synthesis is apparently dependent on the state of carbohydrate metabolism, as is lipogenesis. In vitro, both insulin and glucose — not insulin alone — are necessary for restoration of this process in diabetic tissue. Moreover, the protein synthetic ability of diabetic tissues progressively deteriorates in diabetes, and partial restoration can be effected by as little as ten hours of pretreatment of the donor diabetic animal by both insulin and glucose.[14]

Previous evidence had indicated that normal growth in the hypophysectomized and depancreatectomized animal seemed to require both growth hormone and insulin.[19] Accordingly, even this demonstration of the protein anabolic activity of insulin in diabetes left it with a role distinctly secondary to that of the pituitary gland. Recently, however, Salter and Best,[20] by skillful administration of long-acting insulin to the insulin-sensitive hypophysectomized and depancreatectomized animal, achieved normal growth by this hormone alone; this occurred in all tissues, including the epiphyses. Even though greater than normal growth requires the addition of growth hormone, insulin appears now to acquire greater importance in the process of normal growth. This fact explains more specifically the mechanism of diabetic dwarfism and even raises the question of its secondary participation in pituitary dwarfism itself.

Munro and Thomson[21] reinvestigated the well known "protein-sparing" effect of glucose. Ingestion of glucose by both the normal human being and the rat is accompanied by a prompt reduction in the plasma content of amino acids in a ratio corresponding to their requirement for protein synthesis; this does not occur after fat ingestion. The process lasts two hours. Since glucose ingestion stimulates insulin production, this may be an indirect demonstration in the normal of the insulin-protein anabolic effect discussed above.

Miscellaneous Considerations

Although tocopherol (vitamin E) has no value in the treatment of diabetes mellitus, it does accelerate oxygen consumption in the intact animal and specifically in skeletal muscle. Experimental vitamin E deficiency is accompanied by skeletal-muscle dystrophy. Recent work in rats has shown that pretreatment with alpha-tocopheryl phosphate prevents the rise in blood lactate but not in blood sugar that occurs after epinephrine.[22] In vitro studies demonstrated that this is a peripheral action on muscle, probably an inhibition of the phosphoglucomutase system, which is concerned with the breakdown of glucose-6-phosphate to glucose-1-phosphate.[23,24] It does not affect the corresponding hepatic enzyme.

In the previous review, evidence was offered for the uselessness in diabetes of an elevation of blood sugar level as an accelerator of glucose utilization in

the absence of insulin. It has now been shown that, even in the presence of insulin, a blood sugar concentration as high as 1000 mg. per 100 cc. only doubles the utilization rate of glucose.[25] This reemphasizes the point that even under optimum conditions in vivo the relation between plasma glucose concentration and glucose utilization is much more than a simple mass-action phenomenon. In addition the decreased effectiveness of insulin action in acidosis would further diminish this small advantage of hyperglycemia to the vanishing point.

Hitherto, it has been held that normally ketone bodies were produced in the liver and utilized only in the periphery. On this basis, diabetic ketonemia was attributed solely to hepatic overproduction beyond the utilization capacity of the peripheral tissues. Recent investigations of liver slices in normal and diabetic rats showed that lipogenesis from acetoacetate normally occurs in the liver.[13] This is decreased by fasting or diabetes. The block in this function therefore becomes an added mechanism for ketonemia in uncontrolled diabetes.

Newer studies of the carbohydrate metabolism of the fasting state have delineated more clearly the points of similarity and difference from that of diabetes mellitus. In fasting, as in diabetic liver slices, there are two separate blocks in glucose metabolism and only one for fructose.[26] In both, there is impairment in lipogenesis from acetate,[27] which cannot be restored by the addition of insulin alone.[28] Unlike the diabetic, however, the fasting diaphragm can restore this function fully by the addition of glucose (but not protein or fat) without insulin.[29] Acetate conversion to cholesterol is also significantly decreased by fasting, both in the intact rat[30] and in rat-liver slices.[31] This fasting defect can be restored to normal (unlike lipogenesis[31]) by the addition of any one of the three food constituents, glucose, protein hydrolysates or fat.

Blood Sugar Regulation and Glucagon

The blood-sugar-raising factor discovered in some insulin preparations has been renamed glucagon (from the hyperglycemic-glycogenolytic factor).[32-34] The voluminous literature on this subject probably represents scientific interest rather than its physiologic importance in normal metabolism. The main though not the exclusive source of glucagon in the body is the alpha cells of the islands of Langerhans.[35] It has been crystallized to 70 per cent purity and is probably a polypeptide.[36,37]

Its main action is to produce hyperglycemia by glycogenolysis in liver,[38,39] but not in muscle as epinephrine does.[40] Moreover, the sugar does not arise by gluconeogenesis from protein.[41] As secondary effects, it depresses lipogenesis from acetate and decreases the tendency to ketosis in the diabetic animal.[42,43] Its hyperglycemic action, unlike that of epinephrine, is not blocked by dihydroergotamine.[44] Experimentally, it potentiates the diabetogenic action of such diverse agents as growth hormone, cortisone and ACTH.[45]

The pancreas does not secrete glucagon constantly, either in the normal or in the diabetic animal.[46] Growth hormone of the pituitary gland exercises a trophic effect on the alpha cells,[47] and stimulates the secretion of glucagon.[48,49] Hypoglycemia also stimulates its secretion.[50] Homeostatic defense of the body against hypoglycemia was previously assigned, at least in part, to epinephrine secretion. However, this now becomes less probable since spontaneous recovery from hypoglycemia in the human being is not decreased by epinephrine blocking agents such as hydroergotamine[41] or hexamethonium bromide.[51] This function could conceivably be served by glucagon.

Clinically, Ferner[52] has suggested that spontaneous human diabetes stems from a critical alteration in the normal ratio of alpha to beta cells and their corresponding hormones. Unless a constant secretion and greater action are demonstrated for glucagon in the normal organism this seems improbable. Kirtley et al.[36] have noted that glucagon has a greater hyperglycemic effect in the older, obese and more stable diabetic patients; this may help to account for their lesser tendency to hypoglycemia under insulin treatment.

There is a strain of mice that exhibits a syndrome, beginning at the ninth week of life, characterized by obesity and insulin-resistant hyperglycemia.[53,54] The pancreas shows an increase of alpha and beta cells equally. The latter, although degranulated, have an increased insulin content. The primary defect seems to be a block in oxidation of acetate, with diversion to lipogenesis.[55] This hyperactivity of the alpha and beta cells can be interpreted as an attempt, only partially successful, to compensate for the primary biochemical defect.[56]

Carbohydrate Metabolism

It is obvious that the metabolism of the entire organism is more complex than the sum of all its parts. As an example, the efficiency of carbohydrate metabolism was measured by the glucose infusion rate needed to maintain the normal blood sugar in the presence of adequate insulin after evisceration in both normal and hepatectomized dogs.[57] It was discovered that the presence of the liver increased peripheral utilization of sugar two and a half times. The mechanism is unknown.

The quantitative response of blood sugar to a given dose of insulin varies in both normal and diabetic persons. Bearn et al.[58] have elicited more details of the mechanism by measuring the hepatic venous glucose output by cardiac catheterization. They administered small doses of regular insulin and compared the magnitude of the resultant change (decrease) in this index with that (increase) in peripheral glucose utilization. In the normal person both are relatively equal. Diabetic patients show variations: the young, thin patients demonstrate a greater change in the former. There is an opposite trend in those who are older and obese, with stable disease.

Goodale, Olson and Hackel[59] studied cardiac muscle utilization of glucose, pyruvate and lactate by cardiac catheterization in patients with mild diabetes. Even with a mild deviation from normoglycemic regulation (fasting blood sugar as high as 216 mg. per 100 cc.) heart-muscle utilization of these constituents is strikingly reduced. Reversion to normoglycemia by small doses of insulin promptly restores normal metabolism. Although carbohydrate metabolism accounts for only 30 per cent of the total oxygen consumption of the isolated heart, it may be vital in ischemic states.[60] Thus, I have observed clinically an improvement in angina or intermittent claudication after correction of similar mild hyperglycemia in diabetes. It may even be of critical importance for the injured heart muscle in myocardial infarction in a diabetic patient.

Endocrine Effects on Carbohydrate Metabolism

A stimulating effect of growth hormone on the carbohydrate metabolism of the intact animal had previously been described, but more recently this action has been shown even in the absence of the pancreas.[61] This has now been demonstrated on the isolated rat diaphragm in vitro either directly[62] or by preinjection of growth hormone into the donor animal,[63] in which the effect occurs within an hour or two (but is succeeded and overshadowed by an inhibitory action after three hours). Growth hormone probably activates or liberates insulin normally bound to the tissues, for the effect is lost if over six hours elapse after pancreatectomy.[63] A specific lipoprotein fraction of serum with the same effect in vitro has been isolated.[64] The demonstration of this phenomenon is made more difficult both in vivo and in vitro because of the constant and more potent inhibitory effect, as pointed out below, which is present in all tissues and is probably the more important physiologically.

The inhibitory effect is better studied by measurement of the increase in glucose uptake of the normal and diabetic liver and diaphragm that occurs after extirpation of either the adrenal or the pituitary gland.[63,65,66] Inhibition is independent of the presence of a secreting pancreas.[65] After extirpation of both glands, this action cannot be restored in vitro by the addition of growth hormone and cortisone directly.[67] Instead, both hormones must be given in vivo, and the growth hormone seems dominant in this action. The hormones do not act for three hours and the effect lasts for twenty-four to forty-eight hours, indicating a further conversion by the body into the active humoral substance. This has also been located in a specific fraction of the serum lipoprotein.[64] It is neutralized by direct addition of insulin. Because of this, it can be detected only in diabetic (hypoinsulin) serum. It probably acts normally as a physiologic antagonist to insulin. Bornstein[64] showed that it can also antagonize glutathione synthesis in vitro. This hormonal antagonism was confirmed by the study of a specific area of carbohydrate metabolism—namely, the conversion of acetate to fat in rats.[68]

Another physiological role is revealed by the detection of an increase in its concentration and activity in response to insulin-induced hypoglycemia.[64] It may thus act as an adjunct to glucagon in the homeostasis of blood sugar.

The inhibitory effect of cortisone and growth hormone, separately and together, was also measured in vivo in the dog, the decrease in insulin effectiveness being used as an index (that is, by insulin or glucose tolerance tests).[69-71] The effect took three or more days further to occur, and again the pituitary gland seemed to play the dominant role. In addition a new and interesting observation was made of a limited antagonism of the two hormones. When adrenocortical hormones were given to hypophysectomized dogs in addition to growth hormone, the usual diabetogenic effect of the growth hormones, as measured by the glucose tolerance test, was prevented.[70]

The over-all effect of these two glands on carbohydrate metabolism has been evaluated by means of various technics. The administration of a potent growth-hormone preparation to a diabetic human being resulted in a prompt increase in severity of the diabetes, with little rise in nitrogen excretion.[72] This underlines the concepts that the diabetogenic action of the pituitary gland is essentially peripheral.

The adverse effects of the adrenal gland on carbohydrate metabolism are twofold, but the peripheral action is secondary. Although excess gluconeogenesis is the important mechanism involved, it is still not known what proportions are derived from protein and fat. The former has been easier to measure in man by an increase (after ACTH) of amino acids both in blood and in urine.[73,74] After experimentally administered ACTH or in Cushing's disease, the incorporation of tagged amino acids into protein is decreased.[75] However, as in insulin lack, it is not clear without specially designed experiments whether there is a block in protein synthesis or an increased catabolism. Even the finding of an increased concentration of hepatic amino acid oxidase under these circumstances may indicate only an enzyme response to a need for greater disposal of amino acids and not necessarily the cause of their increased accumulation.[76]

In man, the diabetogenic potency of ACTH or the adrenal steroids is small. This is so whether measured by the effect on the insulin or glucose-insulin tolerance test,[77] or in the production of hyperglycemia.[78] During the course of steroid therapy in over 500 patients, the frequency of any abnormality of carbohydrate metabolism was less than 1 per cent, and the abnormality was readily reversible after cessation of treatment. Moreover, such effects occurred only in susceptible patients[78] (family history of diabetes or prior glycosuria), as in animals.[79]

The relation of the blood glutathione to experimental steroid diabetes has been considered important: the

blood value of glutathione is reduced during the diabetes, which is ameliorated by intravenous administration.[80] In Cushing's disease in human patients its blood level has not been found consistently decreased.[81,82] Moreover, the administration of glutathione aggravates, even to the point of death, the steroid diabetes of rats.[83] This results not from an adverse effect on pancreatic insulin secretion but more probably from a sudden reversal of the glycogenetic effect of steroids with the production of a sudden hyperglycemia.[84]

Pathology and Pathogenesis of Diabetes Mellitus

Further attempts have been made to evaluate the prevalence and significance of certain pathologic findings in the pancreas of human patients with diabetes. In the first place hyalinization of the islets, which has been re-evaluated in a large series of cases,[85] is almost never present when the case is properly diagnosed as nondiabetic. Yet its frequency does not parallel the duration of the disease, increasing with age, to be sure, but even over the age of fifty hyalinization is present in less than 50 per cent of patients. Although pathognomonic of diabetes, it is more probably an accompaniment or complication than the cause. Secondly, degranulation of the beta cells has been studied and found to be increased in younger patients and in those with poor control of the diabetes.[86] This supports its value as an index of exhaustion of islet function and decreased insulin content. It would be interesting to correlate this finding with the new histochemical method of demonstrating the disulfide groups of insulin.[87] Finally, hydropic degeneration of beta cells can be produced in the pancreas of even a nondiabetic rat.[88] It appears under the stress of acute refeeding after the pancreas has been rested by starvation or chronic insulin administration. The food may be a mixed meal, glucose or even fructose or galactose.[89] This decreases further the pathognomonic significance of this finding in diabetes.

Haist[90] has reviewed the factors affecting the islands of Langerhans in rats. He divides them mainly into nutritional and endocrine.[90] Analysis of the former shows that a high-calorie diet stimulates growth of the islets only in proportion to body weight as a whole, whereas a high-carbohydrate diet increases the growth specifically. The pituitary gland has no trophic influence on the islets, for they remain unchanged after hypophysectomy (unlike the gonads).[91] However, saline extracts of the anterior pituitary gland or growth-hormone preparations can produce specific islet growth.[92] This action requires the presence of a functioning pituitary gland, for in its absence these preparations cause islet growth only proportional to that of body growth.

The recognized dynamic qualities of the rat pancreas are further underlined by Lazarow's[79] careful long-term studies of alloxan diabetes in that species. After doses of alloxan so small as not even to yield an abnormal glucose tolerance test, the rats, fed a normal diet, progressed to diabetes in the first year. Then, spontaneously, there was gradual reversion to a state normal even by the glucose tolerance test. This record of waxing and waning of the disease, even though in another species and under specific circumstances, is worth noting, and the mechanism should be investigated. It resembles occasional experiences encountered in human patients with the disease.

Diagnosis

The need for early diagnosis has led to many community surveys. Urine testing is still the most efficient technic for the effort expended, and the new dreypak method seems the simplest.[93] This consists of a combination identification tag and test paper that is wet in the urine, dried and mailed to a central laboratory for testing by immersion in hot Benedict solution and production of the usual colors. The patient response rate of 13 per cent was comparable with other, more protracted methods (24 per cent).[94] The additional use of a blood sugar test naturally increases the sensitivity of detection, but one performed an hour after a meal is less sensitive (1.87 per cent diabetes[95]) than one performed after administration of 50 gm. of glucose (3.4 per cent[96]). A positive result by either would require a follow-up glucose tolerance test. On the other hand, a single blood sugar test two hours after administration of glucose (with a screening level of 150 mg. per 100 cc.) may well be equivalent to a glucose tolerance test; this may turn out to be the best method but has not yet been used for community case finding.[97,98]

In such surveys, the definition of what is an abnormal blood sugar level is to some extent arbitrary. This is an important problem. For example, Wilkerson and Krall,[97] in a follow-up study of a group of patients screened at a blood sugar level of 200 mg. per 100 cc. (after eating) four years previously, found that even in that short period, 31 per cent of those dismissed as normal with a blood sugar level of 170 to 200 mg. per 100 cc. had become diabetic. Moreover, by comparison with this group, those with an original level of 140 to 170 mg. per 100 cc. comprised three times as many potential diabetic patients even though the percentage frequency was less. Thus, even with the simpler methods short of a glucose tolerance test, the sensitivity can be expanded, but with the expenditure of increased effort. The answer may lie in deliberate selection of groups to be tested. For example, even a glucose tolerance method would yield only 1.2 per cent abnormal results below the age of forty-five years,[98] whereas even simpler methods would yield 6 per cent results over the ages of fifty to sixty years.[99,100]

In follow-up studies of patients screened for potential diabetes by blood sugar tests, in surveys in such diverse areas as Massachusetts[101] and Georgia,[95] physicians to whom the subjects returned failed to use proper diagnostic blood sugar tests (glucose tolerance)

or any at all in fully 80 per cent of cases. This reveals a weak element in the medical problem of diabetes control, as well as a great need for educational efforts.

In the definitive diagnosis of suspected diabetes the oral glucose tolerance test leaves much to be desired. The additional determination of blood pyruvate and lactate simultaneously with the glucose tolerance test does not help in borderline cases.[102] It is helpful mainly with the abnormal glucose tolerance curve of Cushing's disease, which, although of great interest, does not solve the important problem in differential diagnosis.[103]

Associated Conditions

Hirson[104] has described 6 cases of localized muscular atrophy of varying degrees of severity in diabetes. These were usually asymmetrical, not at the sites of insulin injection and were without neurologic signs. The mechanism is unknown.

The carbohydrate metabolism of human leukocytes has been studied.[105] A deficient utilization of glucose and decreased production of lactate from glucose occur in leukocytes of diabetic patients and are corrected by proper regulation. The only mechanism so far proposed for the lowered resistance to infection in diabetes has been a decrease in the leukocytic defenses,[106] which may be the underlying basis for this phenomenon.

Disease of the liver may be accompanied by reduced protection from fasting hypoglycemia. The frequency of this feature in a group of patients with recognized liver disease is less than 1 per cent.[107] However, Mellinkoff and Tumulty[108] collected 20 cases of symptomatic hepatic hypoglycemia of varying severity, some fatal. They pointed out that the hepatic disorder is frequently disproportionately mild for the severity of the disturbance in its blood-sugar-regulating function. An increased diagnostic awareness is needed to avoid misdiagnosis of this serious and remediable emergency.

The converse–impaired carbohydrate tolerance in hepatic disease—is still difficult to differentiate from diabetes even with the best of present tests, including the simultaneous determination of blood inorganic phosphorus with the glucose tolerance test.[109] The best method of differentiation at present is the reversal of the metabolic defect with improvement in the liver.

Liver function in diabetes mellitus is reported to be usually normal,[110-114] even by newer tests, such as one, not yet reported, that I have applied, using the serum cholinesterase determination[115] as an index. Abnormal function is reversible with improvement of regulation of the diabetes.[109] Morphologically, fatty infiltration of the liver is exceedingly frequent in adult diabetes and yet is not consistently accompanied by abnormality of function.[110,111,116] It has been both claimed[116] and denied[114,117] that cirrhosis of the liver is more frequent in diabetes.

(To be concluded)

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MEDICAL INTELLIGENCE

PARALYTIC ILEUS FOLLOWING USE OF BANTHINE DURING GASTROINTESTINAL BLEEDING*

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PARALYTIC ileus may occur in many situations. However, it is uncommon in patients with gastrointestinal hemorrhage unless shock, electrolyte imbalance, peritonitis or obstruction is present.

In the 5 cases presented below, paralytic ileus followed the administration of Banthine or pro-Banthine during treatment for gastrointestinal hemorrhage. This sequela of Banthine therapy has not been observed in this hospital unless frank hemorrhage into the bowel has been present. Three of the patients had peptic ulcers, 1 had esophageal varices, and 1 had lymphosarcoma infiltrating the stomach.

CASE REPORTS

CASE 1. F.M., a 65-year-old man, was admitted to the hospital because of weakness and perspiration that had developed during the previous day. These symptoms, that progressed to near fainting, were shortly followed by several large black stools. Weakness, tachycardia and dark stools continued until admission. Physical examination, except for signs of anemia and tachycardia, was negative. The blood pressure was 130/80.

A presumptive diagnosis of duodenal ulcer with hemorrhage was made, and treatment with frequent feedings and administration of antacids was started. Blood transfusions were given on the 2d hospital day. On the 3d day, after continuing melena and epigastric distress, 50 mg. of Banthine every 6 hours was started. After the 3d dose urinary retention developed. The abdomen was distended, and bowel sounds were absent. Catheter drainage of the bladder was established; the drug was discontinued. Thirty-six hours later abdominal distention had disappeared, bowel sounds were normal, and bowel movements were occurring without evidence of further bleeding.

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CASE 2. A.P., a 44-year-old man, was admitted to the hospital because of vomiting of blood, tarry stools and extreme weakness. One year previously the diagnosis of peptic ulcer had been made, and he had been following a loose program of ulcer management. Examination on admission revealed mild shock with tachycardia (rate of 134), a blood pressure of 100/50 and great pallor. The abdomen was flat, without tenderness. The hemoglobin was 5.7 gm. per 100 cc.

Immediate treatment consisted of intravenous infusion of 500 cc. of blood plasma followed by 1000 cc. of whole blood. Frequent bland feedings and antacids were begun, together with 25 mg. of Banthine by hypodermic injection every 4 hours. During the 1st 12 hours in the hospital the patient had frequent, dark, bloody stools. All bowel movements ceased on the 2d hospital day. He was unable to void; the abdomen had become distended. Ten injections of 25 mg. of Banthine were given at 4-hour intervals before the drug was discontinued on the 3d hospital day. X-ray films of the abdomen revealed numerous fluid levels throughout, with gas-filled loops of dilated small intestine. Serum sodium, potassium and chloride values were normal. In spite of continuous gastric suction, abdominal distention and absent bowel sounds persisted for 4 days. On the 7th hospital day the bowels again began to move. The abdominal distention disappeared, and the patient was discharged on the 19th hospital day.

CASE 3. L.S., a 41-year-old man, had complained of pain in the upper portion of the abdomen and back for 4 months. He had entered another hospital 3 days before admission because of vomiting of blood and tarry stools. A presumptive diagnosis of peptic ulcer had been made, and Banthine was given by mouth, together with frequent feedings and antacids. At the end of this 3-day period there was considerable distention of the abdomen, with x-ray evidence of gas in the small intestine. Urinary retention necessitated catheter drainage. Levin-tube suction had failed to correct the abdominal distention, and there were no bowel sounds.

Physical examination showed pallor and abdominal distention, with a few high-pitched bowel sounds. The blood pressure was 150/80, and the pulse 100. Banthine was interrupted, and Levin-tube suction was continued. At the end of 3 days abdominal distention had disappeared, and the patient was able to void urine again. Barium-swallow examination demonstrated a questionable lesion in the stomach that operation proved to be lymphosarcoma, with extensive regional metastases.

Hemorrhage from gastric lymphosarcoma was attended by the physical and radiologic appearance of paralytic ileus after Banthine had been administered. The ileus disappeared 3 days after discontinuation of the drug.

CASE 4. F.N., an 81-year-old man, was admitted to the hospital on February 3, 1953, complaining of hematemesis and melena of 2 days' duration. Five years previously a diagnosis of duodenal ulcer had been made. Two years before admission, after an upper gastrointestinal hemorrhage, subtotal gastrectomy had been performed. He had 4 bleeding episodes since then, and medical management had been ignored. Two days before admission he had a massive hemorrhage in the gastrointestinal tract.

Physical examination revealed pallor and dehydration. The blood pressure was 140/75, and the pulse 84. The abdomen was soft and not distended, and the epigastrium was tender.

The red-cell count was 2,700,000, with a hemoglobin of 5.5 gm. per 100 cc. The nonprotein nitrogen was 46 mg. per 100 cc. Other blood chemical constituents and

electrolytes were normal. An upper gastrointestinal series on the 3d hospital day disclosed a hiatal hernia, patent gastrojejunal stoma and narrowing of the proximal jejunal channel, with no evidence of an ulcer crater.

On admission milk and cream or antacids were given every half hour. Oral administration of Banthine, 25 mg. every 6 hours, was started; the dosage was slowly increased to 75 mg. every 6 hours on the 5th hospital day. Fifteen hundred cubic centimeters of whole blood was given in the 1st 3 days. By the 5th day the stools were guaiac negative. On the 5th day abdominal distention and urinary retention supervened. Banthine therapy was stopped in the morning of the next day. The abdominal distention increased, and the bowel sounds were poor to absent for the next 6 days. Bowel movements remained absent until the 11th hospital day. X-rays were interpreted as showing a pattern of ileus. Gastric suction yielded moderate amounts of fluid without blood. Fluid and electrolyte balance was maintained by the parenteral route. The blood counts remained stable, and the hemoglobin at 10.5 gm. per 100 cc. Urecholine, 2.5 mg. every 4 hours, was given intramuscularly on the 9th and 10th hospital days. On the night of the 10th day the patient expelled large amounts of flatus; liquid stools and gas in copious quantities marked the 11th hospital day and thereafter the abdominal distention rapidly disappeared. The only evidence of further bleeding was on the 15th hospital day. He was discharged on a bland diet and antacids, and was asymptomatic at the last report.

Case 5. K.B., a 30-year-old man, had been under observation in a state mental institution because of schizophrenia. In March, 1953, he sustained an accidental abdominal trauma. He was admitted to the hospital on November 5 because of repeated bouts of hematemesis for 2 months, during which he had been receiving therapy for bleeding peptic ulcer.

Physical examination revealed pallor, mild rigidity of the upper abdomen and pitting edema of the feet and legs. The blood pressure was 117/70. The pulse was 96 per minute and regular. The red-cell count was 3,300,000, with a hemoglobin of 7.5 gm. per 100 cc. The nonprotein nitrogen was 50 mg. per 100 cc. Serum electrolytes were normal. The prothrombin time was 47 per cent of normal.

An ulcer regimen was instituted, including 50 mg. of Pro-Banthine intramuscularly every 5 hours for 5 doses. On the day after admission the abdomen became greatly distended. Urinary retention necessitated an indwelling catheter. X-ray examination of the abdomen on the 2d hospital day showed distention of the small bowel and colon in the pattern of ileus. This persisted for 3 days and gradually subsided, with resumption of spontaneous urination and bowel movements. Mild bleeding persisted.

Later investigations revealed esophageal varices, and bleeding was controlled with a Sengstoken tube. Laparotomy and splenoportograms demonstrated extrahepatic portal obstruction, and splenectomy was carried out. The patient improved clinically and had had no further hemorrhage when last seen 3 months after the operation.

Discussion

It is apparent that the factors common to all these patients comprise paralytic ileus, absence of electrolyte imbalance, urinary retention, male sex, gastrointestinal hemorrhage and Banthine or Pro-Banthine therapy. The patients were observed on three different hospital services whose therapeutic methods vary somewhat.

The paralytic atony of the small bowel was in each case verified by roentgenographic evidence of gas, distention of the abdomen and absence of bowel sounds and of bowel movements. The longest period of atony was six days, and the average was three and a half days.

The absence of electrolyte abnormality is mentioned only to discount this as a contributing factor. Urinary retention, present in all cases, points to a well known effect of Banthine. All these patients were males, possibly as a result of our sampling since 80 to 90 per cent of our patients with bleeding from the upper intestinal tract are males.

Banthine, or methantheline (diethylaminoethyl xanthene-9, carboxylate methobromide), a commonly used and beneficial quaternary ammonium compound, possesses effective anticholinergic and antispasmodic properties.[1] It has been observed experimentally and clinically to reduce markedly gastrointestinal secretions and motility.[2,3] These properties constitute the basis for its use in peptic-ulcer therapy. Kern et al.[4] found that Banthine profoundly depresses sigmoid motility. Its chief side effects, which are also due to its anticholinergic action, include urinary retention, xerostomia and mydriasis. In large doses a curarelike effect accompanied by abdominal distention[5] has been reported.

It is conceivable that if the Banthine effect on gastrointestinal motility were reinforced, paralysis of the small bowel would result. It is our clinical impression that this happened in the 5 cases reported above and that gastrointestinal hemorrhage was the responsible factor. There is no evidence in the available literature that the presence of blood in the intestinal tract can decrease its motility. The role of "shock" and disturbed homeostasis is difficult to evaluate. All patients had probably been in shock before admission and 1 was nearly in shock when Banthine was started. This may have had some effect on the ileus. During the two-year period in which these 5 cases occurred ileus was not observed in this hospital in cases of bleeding from the upper gastrointestinal tract unless anticholinergic or quaternary ammonium compounds such as hexamethonium had been given. Golden,[6] in mentioning "atony and/or paralytic ileus" in 2 patients with ulcerative colitis, gives Banthine as a causal agent. His theoretical mode of action includes increased sympathetic tone as a result of the colon irritation superimposed on a Banthine-induced parasympathetic inhibition to produce small-bowel paralysis. If such a course of events took place, large amounts of blood may have irritated the large bowel and increased the paralyzing effects of Banthine.

It is not the purpose of this paper to show the mechanisms by which ileus was produced; it is rather to point out that it did occur when 5 patients with acute gastrointestinal hemorrhage were given Banthine. This complication increased the morbidity and lengthened the hospital stay. Bleeding seemed to abate during the period of ileus in 4 patients with gastric or duodenal ulcerations, but not in the patient with bleeding esophageal varices.

It should be realized that Banthine and gastrointestinal hemorrhage together may produce intestinal paralysis. This is a physiologic alteration that may be aided by the use of prostigmine or Urecholine. Exploratory laparotomy is not indicated unless mechanical obstruction can be proved.

Summary and Conclusions

Five cases of upper gastrointestinal hemorrhage in which paralytic ileus during Banthine therapy developed are reported. Other causal factors were apparently absent. It is believed that gastrointestinal hemorrhage constitutes a contraindication to Banthine therapy.

A diagnosis of intestinal obstruction indicating surgery should be made with caution in patients with gastrointestinal bleeding under treatment with Banthine.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40421

Presentation of Case

A fifty-year-old dishwasher was admitted to the hospital because of dysphagia.

Six to eight weeks before admission a "head cold," with a slight cough, developed. A few days later pain in the gums occurred, and all the teeth were extracted. About four weeks before admission, five or six days after the extraction was complete, food began to stick in the throat, the dysphagia being associated with a poorly described pain in the region of the thyroid. At first there was only difficulty in swallowing solids, but by the time of admission only fluids and a little coffee-soaked bread were being taken. As the dysphagia grew severe, regurgitation of small quantities of food began. The nature of the material brought up was described variously as undigested food, partially digested food and foul-smelling, yellowish-green matter. During the weeks before admission the patient's weight fell from about 100 to 85½ pounds.

Since early childhood the patient had been troubled by periumbilical pain several times a day, which was unrelated to meals but relieved by sodium bicarbonate. The intake of sodium bicarbonate was so large that eleven years before admission he had been seen in the overnight ward with muscular cramps and paresthesias that were believed to be due to tetany caused by overindulgence in alkali. Four months before admission he gave up the sodium bicarbonate, apparently with some improvement in the abdominal symptoms. Four or five years before admission the proximal interphalangeal joints of several fingers became swollen. In the three or four months before admission the skin of the hands became smooth and shiny—a change that he attributed to his having become a dishwasher at that time. In the month before admission there were episodes in which the hands became cold, but there was never pallor or cyanosis. For several years the intake of alcohol had been high, though in recent years it had become more moderate.

Physical examination showed a cachectic man. The mouth and throat were normal. The trachea was in the midline, and there was slight tenderness when it was moved from side to side. The lung fields were clear. The heart was not enlarged; the aortic second sound was louder than the pulmonic, and there was a soft, blowing systolic murmur loudest at the apex. The abdomen was normal. The skin of the hands was smooth, shiny and dry and appeared waxy. There was moderate swelling of the proximal interphalangeal joints of all fingers, with slight limitation of movement.

The temperature was 98°F., the pulse 84, and the respirations 18. The blood pressure was 104 systolic, 78 diastolic.

The urine gave an olive test for sugar and was otherwise normal. Examination of the blood revealed a hemoglobin of 14.0 gm. per 100 cc. and a white-cell count of 12,600, with 76 per cent neutrophils, 14 per cent large lymphocytes, 6 per cent small lymphocytes and 4 per cent monocytes. The serum sodium was 137 milliequiv., the potassium 4.1 milliequiv., and the chloride 105 milliequiv. per liter; the nonprotein nitrogen was 40 mg., the albumin 3.1 gm., the globulin 2.9 gm., the cholesterol 214 mg., the fasting blood sugar 68 mg., and the alkaline phosphatase 1.4 units per 100 cc. The prothrombin time was 100 per cent. After the ingestion of 100 gm. of glucose by mouth, the blood sugar, which had been 82 mg. fasting, rose to 151 mg. in half an hour, 192 mg. in one hour, 206

mg. in two hours, 174 mg. in three hours and 138 mg. per 100 cc. in four hours. After intravenous administration of 17 gm. of glucose the blood sugar rose from a fasting level of 76 mg. to 124 mg. in half an hour, 89 mg. in one hour, 62 mg. in one and a half hours and 73 mg. per 100 cc. in two and a half hours. It was noticed that the urine gave a green test when collected during the last hour of the intravenous glucose tolerance test. The blood Hinton test was negative. An electrocardiogram disclosed a normal sinus rhythm at a rate of 100, a PR interval of 0.08 second, a QRS interval of 0.08 second, very high precordial voltages, generally sagging ST segments and low T waves. It was interpreted as showing myocardial damage. A barium-swallow examination demonstrated a constriction 12 cm. above the cardia (Fig. 1). The mucosa immediately above the stricture was smooth and tapering. More proximally, the esophagus was dilated. No peristaltic waves were seen. The whole of the distal part of the esophagus was constricted. The constriction allowed a trickle of barium to pass, but at no time dilated. The mucosa in the constriction was either destroyed or grossly deformed. Insufficient barium reached the stomach to permit an adequate examination, but films suggested an area of constriction in the antrum extending for at least 3 cm. A film of the chest was unremarkable. Slight swelling of the soft tissues around the proximal interphalangeal joints was seen, but a film of the joints revealed no abnormality.

Esophagoscopic examination showed a stricture in the middle third of the esophagus. The mucosa of the esophagus was smooth so far as it could be seen. The stricture was easily dilated from the size of a No. 14 to that of a No. 26 bougie. Two biopsies were taken. Each disclosed chronic inflammation. Attempts were made to get the patient to swallow a thread, but without success. Another esophagoscopic examination with a dilatation was performed, but x-ray examination of the stomach was unsuccessful. On one occasion a Levin tube was passed, and 50 cc. of bilious material was aspirated. Free acid was present. Cytologic examination was unsatisfactory. On the thirty-eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Laurence L. Robbins*: Being a radiologist, I cannot discuss this case adequately from the clinical standpoint. In the first place I need some help about the interpretation of the glucose tolerance tests in this man, who had a diabetic curve on the oral and a relatively flat curve on the intravenous test.

Dr. John B. Stanbury: I suppose that the contradiction was due to a delayed rate of absorption caused by the obstruction. The patient could take care of the sugar once it arrived in the blood.

Dr. Jacob Lerman: Delayed absorption lowers the blood sugar and gives a flat curve, as in myxedema.

Dr. Robbins: Does the blood sugar go up in the oral test?

Dr. Stanbury: It goes up quite well.

Dr. Russell Frasier: I should be inclined to believe that in the esophagus the glucose only seeped through, thus prolonging the absorption.

Dr. Robbins: That helps me. I am going to disregard the possibility of diabetes.

This fifty-year-old man suddenly had dysphagia, which progressed over a period of four weeks, and considerable weight loss. What the slight head cold and sore gums meant, I do not know, but in any event the teeth were removed. At first I thought that the fact that he did not have teeth might have been a factor in the dysphagia, but the x-ray films ruled that out. Swollen hands and painful joints in the fingers suggest pulmonary osteoarthropathy, and it is well known that many patients have had their teeth pulled before the correct diagnosis is made.

I do not think I am going to learn much from the films to explain the various pains that were more or less epigastric for which the patient took sodium bicarbonate over the years, for an adequate examination of the stomach could not be done. It simply means that he had considerable discomfort in the gastrointestinal tract for years and had treated himself for it. The shiny skin, swollen hands and swelling around the proximal interphalangeal joints apparently raised the question of scleroderma. The x-ray findings in scleroderma, in addition to an edematous appearance of the soft tissue, frequently include changes in the terminal phalanges, with a tendency to become pointed. I do not see anything abnormal in the films of the hands. There is slight swelling around the proximal phalangeal joints. If somebody wanted to say that this was early rheumatoid arthritis I would not argue, but I am certainly not impressed by those hands. I tried at first to make the diagnosis of osteoarthropathy, since there is some calcification in the interosseous membranes, but I think it is confined to those membranes, and I see no real periosteal change.

In the first examination (Fig. 1), the esophagus is either normal or dilated in all the films from the cervical area down to the level of the bifurcation of the trachea; from there to the diaphragm it is irregularly narrowed. It is narrower about 6 cm. below the bifurcation and then appears to widen out. It contains something within its lumen, which is almost 1 cm. in its anteroposterior diameter, and then narrows again. It appears to be narrowed as it goes through the diaphragm. In the protocol it is noted that there is narrowing of the distal portion of the stomach. On this single film I see that narrowing but beyond that I do not believe I can say anything. Of course, there could be a scirrhous carcinoma involving the stomach, but I have no right to say so on the incomplete examination shown.

In the second examination, done nearly a month

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later, there is no essential change in the esophagus. One thing that I should like to point out—and it shows up a little better on this film than it did on the original—is that there is not only narrowing of a long segment of the esophagus but also evidence of either thickening of its wall or mediastinal involvement. Normally, there is only 2 or 3 mm. between the pleural reflection on the right side of the mediastinum and the lumen of the esophagus. In fact one can really call that the esophageal wall when one sees it on the films. In addition there is thickening of the posterior reflection on the left side of the mediastinum, again indicating that there is something abnormal there. Moreover, there tends to be a lobulation of those lines that suggests the possibility of lymph-node enlargement or masses in the involved area. A film of the chest taken a few days later merely shows that the lung fields are, for practical purposes, clear. There may be a slight change in the markings.

DR. WALTER BAUER: Can you see enlarged lymph nodes?

DR. ROBBINS: This film is not sufficiently penetrated to show them. The overexposed films suggest what might be the periesophageal lymph nodes.

I have the question of scleroderma put before me. As far as I can see from the films, if this was scleroderma it resembles no case that I have seen. Usually, the esophagus is widened more or less throughout its course, and there is absence of peristaltic action and great delay in emptying. There may be a slight dilatation just above the diaphragm, and just below the dilatation there is an area of narrowing supposedly due to fibrosis. That is the more or less typical x-ray appearance of scleroderma of the esophagus.

The other benign condition to be considered, particularly with the long history of the use of sodium bicarbonate, is the syndrome, which Dr. Benedict knows so well, of duodenal ulcer, hiatus hernia and esophageal ulceration. That is a possibility, but along with that I should expect a perforation of an esophageal ulcer producing a low-grade mediastinitis to give this appearance. A stricture due to a chemical such as lye or hydrochloric acid is usually much more localized. Furthermore, there was no history to suggest it. There is no reason to suspect a rupture of the esophagus from trauma or prolonged vomiting, and, again, there is nothing in the history to suggest such a diagnosis.

The first tumor that I must consider is, of course, carcinoma. Could this have been a carcinoma of the esophagus itself? Yes; and the distribution of enlarged lymph nodes would be quite consistent. If I had to place a carcinoma of the esophagus itself, without being able to see the esophagus as well as I should like, I should say that the primary tumor would have been in the lower third, with lymph-node involvement apparent upward as well as downward below the diaphragm. It is possible that the narrowing of the stomach was due to lymph-node involvement. We have seen such changes in carcinoma of the esophagus several times.

Could this have been carcinoma of the cardia or fundus of the stomach, with extension up the esophagus? That may be why it was not diagnosed on esophagoscopic examination. This is no fault of the endoscopist—the tumor grows in such a way that it frequently extends submucosally up the esophagus for a considerable distance, so that a biopsy at the time of esophagoscopic examination may not be deep enough to reach the tumor and is consequently reported as showing only chronic inflammation.

FIGURE 1. *Barium Examination of the Esophagus, Showing Narrowing of the Lumen of the Lower Portion of the Esophagus, with Thickening of the Wall of the Esophagus. There is a questionable deformity of the fundus of the stomach.*

I should not consider lymphoma. I have seen only 2 cases of lymphoma that appeared to be primary in the esophagus; those were much more localized than this.

The mixed tumors, the carcinosarcomas, if one accepts such an entity, have to be considered.

I did not mention extrinsic varices. The changes seen in the inside of the esophagus could not have been due to intrinsic varices, but we have seen varices in the outer coats of the esophagus that have produced this lobulation. I consider that unlikely.

I cannot believe that Dr. Castleman would give me a case that is an out-and-out simple carcinoma of the esophagus, so that there must be something else. Actually, from the findings given and the x-ray appearance I can simply say that there is an area of narrowing of the lumen of the esophagus, with evidence

of protrusion of tissue into the narrowed lumen, and that there is involvement extrinsically of the esophagus and mediastinum. Although a benign ulcer with rupture of the esophagus and mediastinitis are definite possibilities, I believe this was a malignant tumor, probably a carcinoma.

DR. BAUER: I wish to thank Dr. Robbins for his complete discussion of the differential diagnosis of esophageal lesions based on roentgenographic examination. I should next like to say that we all have our days when we are one-track minded, and this, I believe, is one of mine. I think this man had either dermatomyositis or scleroderma. I favor the latter diagnosis for a number of reasons. First of all, I think I am right in saying that in the series of cases reported by Hale and Schatzki* the esophageal involvement was as extensive as this. Is that true, Dr. Robbins?

DR. ROBBINS: No; it is not.

DR. BAUER: Secondly, esophageal involvement is more frequent in scleroderma than in dermatomyositis. Thirdly, nothing in the history suggests that the patient had dermatomyositis. He had no fever and no involvement of the skin, subcutaneous tissue or muscle. Occasionally, the first complaint of the patient with dermatomyositis is that he cannot go upstairs with ease because of quadriceps-muscle involvement and the attendant weakness. In other cases the disease may begin in the arms. This man was very cachectic. Dr. Castleman's abstractor does not tell us how much weight was lost or over how long a period.

DR. ROBBINS: Fourteen pounds was lost in four weeks.

DR. BAUER: That is a very rapid development of cachexia.

This man had a history of articular involvement four or five years previously. On several occasions we have made a diagnosis of rheumatoid arthritis only to realize three to five years later that it was scleroderma with periarticular involvement and not rheumatoid arthritis. In the end stage of scleroderma there may be considerable periarticular fibrosis of the interphalangeal joints and marked limitation of motion and atrophy of the muscle about the phalanges, thereby giving the impression that the joints are swollen, though in reality they are not.

I think it is important to recognize that scleroderma is a generalized disease. On rare occasions the gastrointestinal involvement, either esophageal or small-bowel or both, may be present for years before involvement of the subcutaneous tissue is evident. I remember a patient first seen by Dr. Chester M. Jones about twenty years ago because of difficulty in swallowing and bilateral ankle involvement. At that time the patient was seen by one of the arthritis study group, and a diagnosis of rheumatoid arthritis was made. The ankle involvement subsequently disappeared. The esophageal symptoms persisted despite all forms of treatment and was still a dominant complaint when I saw the patient two years ago. About six months before this hospital entry the patient exhibited the classic signs of scleroderma, including skin atrophy, pigmentation and cachexia. Dr. Benedict saw her in consultation and relieved her difficulty in swallowing, but unfortunately she did not continue the bougienage treatment.

I believe that the esophageal lesion in the case under discussion was a manifestation of scleroderma.

DR. ROBBINS: I do not mean to imply that the patient did not have scleroderma clinically, but I do not believe that the esophageal lesion was scleroderma.

DR. BAUER: Was a small-bowel examination done on this patient?

DR. BENJAMIN CASTLEMAN: Barium would not pass through the narrowed esophagus.

DR. EVAN CALKINS: Do you not think that the cardiac change could have been on that basis as well?

DR. BAUER: Yes. It is of interest and perhaps of diagnostic importance that in this case there was no evidence of pulmonary fibrosis.

DR. ROBBINS: Not enough to call it scleroderma. I looked at the film of the chest with this in mind very carefully. Furthermore, I have never seen scleroderma of the stomach although I have seen it in the small bowel several times.

DR. BAUER: I do not remember that gastric involvement has ever been described in scleroderma.

I think this man exhibited cachexia before the four weeks mentioned. What made him so cachectic in four weeks?

DR. JOSEPH C. AUB: Not eating.

DR. BAUER: Did he only weigh 100 pounds in his prime?

DR. EDWARD B. BENEDICT: As I remember, this man was extremely thin whenever I saw him.

DR. BAUER: But you saw him when he was very sick.

DR. BENEDICT: He was a very small man; there was no question about that.

DR. BAUER: Did he have a pinched nose?

DR. BENEDICT: I do not remember.

DR. BAUER: Could he protrude his tongue, wrinkle his forehead and smile with ease? If so, I doubt if he had scleroderma.

DR. BENEDICT: You expect me to remember a great many things.

DR. BAUER: There was a possibility of scleroderma; when you saw him I thought you might have observed some of these abnormalities caused by the cutaneous sclerosis.

DR. BENEDICT: The findings on esophagoscopic examination did not look at all like scleroderma; they looked like a benign stenosis with a very smooth upper margin. All one can see of such a lesion by esophagoscopic examination is the upper margin. A negative

*Hale, C. H., and Schatzki, R. Roentgenological appearance of gastrointestinal tract in scleroderma. *Am. J. Roentgenol.* 51:407-420, 1944.

biopsy, although we try to take it from far down inside the lumen of the stenosis, does not rule out carcinoma. We have had occasional cases of achalasia and occasional stenoses of the esophagus, treated as benign lesions, in which carcinoma of the stomach was eventually found. As Dr. Robbins pointed out, the condition in the esophagus under such circumstances may look entirely benign by esophagoscopic examination, but a deep submucosal biopsy may reveal carcinoma.

Clinical Diagnosis

Benign esophageal stricture.

Dr. Laurence L. Robbins's Diagnosis

Carcinoma of esophagus, with lymph-node involvement above and below diaphragm.

Anatomical Diagnosis

Carcinoma of stomach, with extension into esophagus and with metastases to regional lymph nodes.

Pathological Discussion

Dr. Castleman: Because of the history of the substernal burning and the taking of alkalis the surgeons thought that the patient had the syndrome of duodenal ulcer, hiatus hernia and peptic ulcer of the esophagus with stricture; that was the preoperative diagnosis, after the two negative esophagoscopic examinations. The abdomen was then explored, and the stomach was found to be very small and contracted, with the greater curvature adherent to the colon; there were enlarged lymph nodes all over the abdomen. One lymph node was biopsied and showed a characteristic signet-ring-cell carcinoma. This is the type of carcinoma that spreads submucosally, just as Dr. Robbins described. I reviewed the esophageal biopsy, which was made up entirely of stomach epithelium, so Dr. Benedict got down quite far. After recutting it serially half-a-dozen times I found one or two cells that were probably signet-ring cells, but there were so few cells that it would be hazardous to make that diagnosis. The patient went home last December, and so far we have not heard anything from him.

Dr. Bauer: I wish to add that the remark "live and learn" is most appropriate on this occasion. In this case I have learned three lessons: it does not pay to have a one-track mind too often; I do not think I shall forget this case; and I shall consider the possibility of cancer of the stomach when I next see a patient presenting this clinical picture and the changes shown on roentgenographic examination described by Dr. Robbins in this man's esophagus.

Dr. Castleman: And the fourth, when Castleman puts on a clinicopathological conference the diagnosis may be, contrary to Dr. Robbins's implication, an "out-and-out, simple carcinoma."

CASE 40422

Presentation of Case

A fifty-six-year-old Canadian-born widower was admitted to the hospital because of shortness of breath.

He had been generally well until two years before entry, when he began having frequent upper respiratory infections, and his usual morning cough became worse. The cough was productive of a cupful of green-yellow sputum daily, mostly in the morning. He had been able to continue working as a shipping clerk until a month before admission, when he had a "chest cold." This was accompanied by slight dyspnea and further exaggeration of the morning cough. He noted for the first time that the sputum was blood streaked, and occasionally he expectorated fingernail-sized blood clots. The cough, dyspnea and hemoptysis persisted for the next several weeks. Three days before admission a dull, persistent pain appeared in the right lower anterior part of the chest. The pain was not pleuritic, disappeared for a short time after a day, recurred and persisted until admission. The patient denied any chills or fever, although he had had occasional night sweats in the past month. He had lost about 25 pounds in the past month. He did not know of any exposure to tuberculous patients.

Twenty years before admission he first began having autumnal asthma, which soon became related also to upper respiratory infections and for the past several years had been present throughout the year. He denied any known allergy or hay fever. Twenty-five years previously he had been treated at home for pneumonia. As a boy he had had whooping cough. He had smoked 5 to 10 cigars daily until three years previously, when he had stopped smoking. The father had died at the age of seventy-three of "asthma," and the mother at the age of seventy-three of hypertension; 1 of 2 siblings had asthma.

Physical examination revealed a well developed man with warm, sweaty skin and rapid respirations. The tonsils were large and injected. The thyroid gland was approximately one and a half times the normal size and smooth throughout. A fine tremor was noted in the tongue and outstretched hands. The anteroposterior diameter of the chest was increased, and chest expansion was diminished. The right base and right lateral side of the chest were dull to flat to percussion. There were moist rales and bronchial, almost amphoric, breath sounds in the right axilla. Tactile fremitus was diminished over the same area. There was an apical gallop rhythm; otherwise, the heart was normal. An easily reducible inguinal hernia was present on the right. There were moderate clubbing of the fingertips and cyanosis of the nailbeds.

The temperature was 103°F., the pulse 132, and the respirations 36. The blood pressure was 150 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood disclosed a hemoglobin of 17.8 gm. per 100 cc. and a white-cell count of 19,000, with 83 per cent neutrophils. Blood culture was negative. Repeated sputum cultures demonstrated an abundant growth of *Haemophilus influenzae*, a few alpha-hemolytic streptococci and rare colonies of *Staphylococcus albus*. A tuberculin skin test with first-strength purified protein derivative was negative, as was a concentrated sputum smear for tubercle bacilli. Roentgenograms of the chest showed a large infiltrate in the right middle lobe and slight reduction in the size of the lobe. There was a cavity with a fluid level in the lateral portion of the right middle lobe. A tuberculous scar was noted in the left first interspace, and calcified nodes were observed in the left hilus. The heart was normal in size. Five cytologic examinations of the sputum for tumor cells were "unsatisfactory," one was "doubtful," and two were "negative."

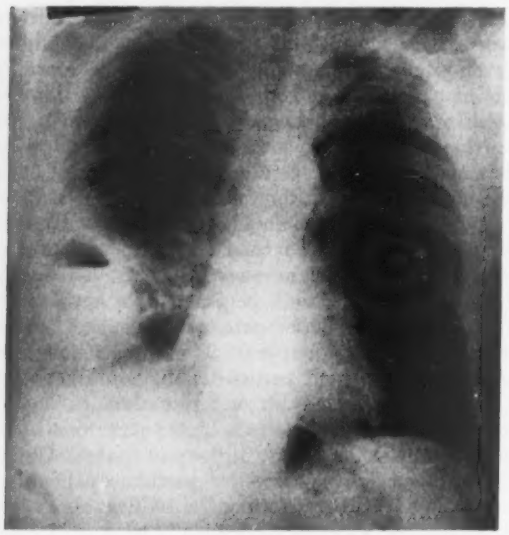

FIGURE 1. *Roentgenogram of the Chest, Showing Thick-Walled Cavity with Fluid Level in the Lateral Segment of the Right Middle Lobe.*

The patient was given spasmolytics, penicillin and Gantrisin. There was little if any improvement. The temperature remained elevated for the first week. Chloramphenicol was substituted, followed by slow and slight improvement. He became less dyspneic, although amphoric breath sounds and fine crackles persisted in the right axilla. A week after admission the spleen was palpable just below the left costal margin, and atrial fibrillation was noted. A film of the chest showed that the fluid-containing air pocket in the lateral portion of the right middle lobe had enlarged and that the walls of the cavity measured up to 2 cm. (Fig. 1). The right hilar shadow was somewhat fuller than normal. There was an old fracture in the right seventh rib; in the left ninth rib in the anterior axillary line a small lesion consistent with either osteolysis or an old fracture with surrounding callus was noted. Bronchoscopic examination disclosed marked narrowing and fixation of the orifices of the middle and lower lobes. A biopsy of this area revealed no cancer. Cytologic examination of the washings obtained at bronchoscopy was negative for tumor cells, and a smear showed no acid-fast bacilli. The dyspnea gradually improved so that the patient was able to climb two flights of stairs without discomfort, the cyanosis disappeared, and he felt much better. There were still audible wheezes at the base of the right side of the chest. A film of the chest demonstrated great reduction in the size of the lung lesion, the cavity now measured 1.5 by 3 cm. On the thirtieth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR S. PIER, JR.*: This fifty-six-year-old man evidently had had asthma a good part of his life and undoubtedly had some emphysema. Two years before admission overt symptoms of bronchiectasis, with the production of large amounts of purulent sputum, developed. Then a month before admission he suddenly became acutely ill, began to cough up blood-streaked sputum and raised blood, and had fever, cyanosis and dyspnea. He came into the hospital prostrate, with pneumonia and a large lung abscess. After treatment for a month he seemed much better. I do not think that I can attach much significance to the history of asthma and emphysema except to say that they made him a poor surgical risk for any extirpative process in the lungs. I think I shall ask for help from the x-ray films.

DR. C. C. WANG: The two examinations of the chest show a large, poorly defined infiltration and a fluid-containing cavity in the lateral segment of the right middle lobe. The whole wall of the cavity appears smooth inside and measures at least 2 cm. in thickness (Fig. 1).

DR. PIER: Can you tell anything about the lymph nodes in the hilus?

DR. WANG: There is some prominence of the right hilar shadow, but I do not see definite evidence of enlarged lymph nodes. There is a small lesion in the ninth rib, which appears to be a healing fracture. No definite bone destruction is noted. There are tuberculous scars in the left apex and calcification in the left midlung field and hilus.

DR. PIER: Definitely old tuberculosis?

DR. WANG: Definitely an old process.

DR. PIER: I think that is interesting in view of the negative tuberculin test.

DR. WANG: There is no fluid in the pleural cavity, and on fluoroscopic examination the diaphragm moved well.

DR. PIER: Obviously, on entry this man had a

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large lung abscess. He had hemoptysis for a month before entry, which may be attributed to the lung abscess. It would be interesting to know whether, as he got better, the hemoptysis disappeared. If it did not disappear I shall have to consider more seriously an intrinsic bronchial lesion such as a tumor. Did the hemoptysis lessen?

DR. BENJAMIN CASTLEMAN: There is no statement to that effect in the record.

DR. PIER: The next point that interests me is the large spleen that was palpable after a week in the hospital. One wonders what had caused the spleen to enlarge suddenly. Certainly, acute infectious processes involving the reticuloendothelial system — such as malaria, kala-azar and undulant fever — can cause an enlarged spleen; however, there is no evidence of any of these. Other infectious diseases such as syphilis, tuberculosis and endocarditis may produce an enlargement of the spleen. I wonder whether the spleen really became larger during this first week or whether it was felt only for the first time. When the patient was admitted he was very ill, was breathing rapidly and may have been too sick to co-operate well, so that on the examination the enlarged spleen may not have been felt.

DR. HELEN S. PITTMAN: Dr. Yang Wang was the resident who was asked to palpate the spleen; he has the reputation for being able to feel spleens that nobody else can. I think your interpretation may be right — that Dr. Wang palpated the abdomen and noted the spleen after the patient had been in the hospital for a week.

DR. PIER: Another point I wondered about was whether the spleen receded as the patient improved. Could pulmonary sepsis alone have caused a large spleen? I think it could not unless there was a great deal of sepsis and bacteremia. If the spleen receded as he got better, however, one would have to consider that possibility. Another cause for a large spleen in a man of this age is cirrhosis, for which there is no evidence, however.

The third interesting feature, and I think the crucial part of this case, is that the bronchoscopic examination showed a narrowing and fixation of the orifice of the right-middle and lower-lobe bronchi. Usually, fixation means cancer. I think it is possible for a severe chronic inflammatory process to narrow and fix bronchial orifices. What inflammatory processes could do it? Tuberculosis could if the lymph nodes in the hilus were involved, and the bronchial walls were secondarily invaded. However, active tuberculosis in this man seems remote: he had a few old tuberculous scars, but the bronchoscopic examination did not reveal endobronchial tuberculosis; the sputums were repeatedly negative for tuberculosis; and the tuberculin test was negative. Syphilis has to be considered although it is rare in this location; is there any report of the serologic examination?

DR. CASTLEMAN: It is not recorded.

DR. PIER: Sarcoidosis is another remote possibility, but I think it would be unlikely to cause fixation and narrowing of the bronchi since sarcoid nodes do not caseate or invade in the sense that tuberculosis or cancer do. There is nothing suggestive of a fungous infection. The sputum showed no fungi or yeast. I shall discard a chronic inflammatory process, and that brings me to the question of tumor.

The first tumor to consider is bronchogenic carcinoma. The physicians caring for the patient did their very best to rule that out and did it quite satisfactorily. Cytologic examinations of the sputum were consistently unsatisfactory or negative; one was doubtful, but I think doubtful means nothing in the presence of pulmonary infection. The important thing is that there were no malignant cells. Bronchoscopic examination disclosed no actual tumor; biopsy of the affected area revealed no cancer; and the bronchial washings contained no cancer cells, so I should be rash to make a diagnosis of bronchogenic carcinoma although the fixation and narrowing certainly suggest it.

The most likely possibility is an extrinsic process involving the lymph nodes in the hilus around the bronchi. When I first read the protocol I thought of malignant lymphoma, but since this illness had probably been going on for two years — at least symptoms of bronchiectasis had been present for two years — I think a highly malignant lymphoma would have debilitated the patient more by this time and would have created some anemia. Of the lymphomas I should favor Hodgkin's type, involving the right hilus, mediastinum and spleen. Hodgkin's disease with its inflammatory pathology — necrosis, fibrosis and cellular infiltration — could easily account for narrowing and fixation of the bronchi, and after this time he may have been as well as he seemed after the abscess had largely healed. Hodgkin's disease could account for the negative tuberculin test.

My diagnosis is lymphoma of Hodgkin's type, resulting in bronchial fixation and obstruction, with pneumonia and lung abscess. I suppose the operation was a biopsy.

A PHYSICIAN: I should like to ask whether the stools were examined for amebas and whether there was a history of exposure to sheep or dogs.

DR. CASTLEMAN: There was no mention of either.

A PHYSICIAN: Could this have been due to intrabronchial tuberculosis?

DR. PIER: I think that there would have been some evidence of that on bronchoscopic examination and on the sputum studies; that is why I had discarded that.

DR. EARLE M. CHAPMAN: I wonder if Dr. Pier considered that this might have been an abscess beyond a point of mechanical obstruction, produced by a chronic constricting process, without tuberculosis or cancer.

DR. PIER: I think it could have been, but I was

trying to explain the fixation seen on bronchoscopic examination, and the large spleen.

DR. CASTLEMAN: It is interesting that the interpretation of the first x-ray film was that this represented either a pyogenic or a tuberculous abscess, though the location greatly favored a bronchogenic carcinoma. Carcinoma could not be ruled out. The physician who interpreted the second set of films thought that the osteolytic lesion was probably a metastasis. Is that correct, Dr. Wang?

DR. WANG: That is correct.

DR. CASTLEMAN: Therefore he thought that it was probably a carcinoma of the lung with metastases. For that reason the physicians sent the patient for radiation treatment. The radiologist, however, did not believe that the evidence was strong enough to accept this patient for treatment with a presumptive diagnosis of carcinoma of the lung, and preferred to defer treatment. That was after Dr. Benedict had done the bronchoscopic examination.

DR. EDWARD B. BENEDICT: Dr. Pier is correct; the narrowing and fixation of the bronchus usually does mean a carcinoma; however, I have seen it occur in tuberculosis and in inflammatory diseases without cancer or tuberculosis. In this case there seemed to be extrinsic pressure because there was not very much to see in the bronchus itself. My opinion was that the extrinsic pressure was due to carcinoma.

DR. CASTLEMAN: Since the radiologists had decided not to treat this patient he was sent to the Pulmonary Clinic, where Dr. Pittman saw him.

DR. PITTMAN: Yes; I saw him, and also he was shown at pulmonary rounds. There were two distinct problems: Why did this man have a large abscess, and, in view of the lung changes, how should the situation best be handled? There was always the question of whether this was an abscess behind a carcinoma. Some physicians firmly considered an underlying carcinoma; I took the other side and thought it was only an abscess. Apart from the difficulty in diagnosis, if this man did have a chronic abscess, what could be done about him? I suspect that is one reason why the case is being discussed today. What could be done to improve the condition in a man with limited respiratory reserve without making him a worse respiratory cripple? The question that was put to the Service was whether the patient should have a cavernostomy, which is an operation that is done very rarely today. This was discussed at great length, and Dr. Scannell made a long note about his choice.

DR. J. GORDON SCANNELL: I think you had better let me read that long note because I do not remember it.

DR. PITTMAN: You gave many excellent reasons.

DR. SCANNELL: I hope they are correct!

Apparently, I favored drainage of this abscess for the following reasons: I thought the diagnosis was less likely to be carcinoma than chronic infection because of the x-ray appearance and the failure to demonstrate a lesion on endoscopic examination. The patient was a poor risk from the point of view of the fixed, rigid chest and also the evidence of emphysema. The process failed to clear during a reasonable period of hospitalization and had not drained well into a bronchus; therefore, it seemed wise to establish drainage. If later resection proved necessary after drainage, we could remove a minimal amount of lung. Finally, the area was a satisfactory one to drain—the lesion lay low in the axilla and could be drained comfortably for the patient. In general one likes to excise an abscess cavity, but under the circumstances drainage seemed to be the reasonable procedure. I think I should still abide by that reasoning.

CLINICAL DIAGNOSIS

?Lung abscess.
?Bronchogenic carcinoma.

DR. ARTHUR S. PIER, JR.'S DIAGNOSES

Malignant lymphoma, Hodgkin's type, of bronchial lymph nodes, with fixation and obstruction of bronchus.
Pneumonia.
Pulmonary abscess.

ANATOMICAL DIAGNOSIS

Lung abscess.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. George Richardson, who operated on the patient, removed the ninth rib and found thickened pleura; he inserted a needle in the lung in several places and could not aspirate any pus. The pleura was finally opened, and the lung was found firmly adherent to it over the area seen on the x-ray film. Aspiration still did not yield any pus. An x-ray film was taken to be sure that that was the correct spot; it was, so he assumed that the abscess had drained itself through a bronchus because there was no free pus. A drainage tube was inserted. The patient left the hospital feeling very well. Several months later he came back to have a hernia repaired, and is now being followed in the Out-Patient Department.

DR. PIER: Does he still have a large spleen?

DR. CASTLEMAN: I do not know.

DR. PITTMAN: What was the day of the operation?

DR. CASTLEMAN: The thirtieth hospital day.

DR. PITTMAN: This brings up an important point. I made a note that he had failed to respond to medical therapy, yet, when I look at the films now I realize that no films were taken a short time before the chest was opened. The previous film was taken twelve days before operation. It might have been very instructive to have had a film taken on the twenty-eighth or twenty-ninth hospital day.

DR. SCANNELL: I happened to drop by the operat-

ing room at the time of the operation, and I can assure you that the same thought occurred to the surgeon.

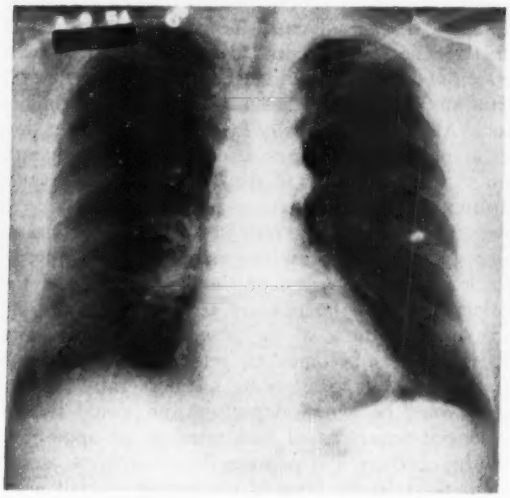

FIGURE 2. *Roentgenogram of the Chest Three Months after Operation, Showing Only Minimal Residual Scarring in the Right Middle Lobe.*

DR. CASTLEMAN: The patient was seen five months after operation and felt well. I think we can assume that this was a lung abscess. The process had cleared as shown in the x-ray films.

DR. WANG: This x-ray examination done three months after operation shows some thickened pleura and only a few scars in the right middle lobe. The hilar shadows remain unchanged (Fig. 2).

DR. CHAPMAN: Dr. Pittman, did you observe this patient postoperatively with the bronchoscope to see if the narrowing was still present in the lower-lobe orifice?

DR. PITTMAN: That point is well taken; apparently, such a study has not been made so far. I shall make a suggestion on the record that it be scheduled after the patient's next clinic visit.

DR. SCANNELL: How can you be sure that this was a lung abscess and not a local pleural pocket or empyema?

DR. CASTLEMAN: If this had been an empyema one would have to assume that there was a fistulous tract in the lung, since the patient was coughing up a great deal of sputum. No tract was found at the time of operation.

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PRIMARY TUBERCULOSIS IN CHILDHOOD

THE problem of tuberculosis in infancy and early childhood is a complicated one. The introduction of effective chemotherapeutic agents has resulted in a great reduction in the mortality in patients with forms of the disease that are known to be highly fatal. All these potentially fatal forms, however, begin as primary complexes associated with implantation of the organism and the development of hypersensitivity to its products, as manifested by positive tuberculin tests. Since only a small proportion of those with the skin-sensitizing exposure have progressive lesions, the problem of the management of the patient who has the primary complex but does not have manifestations of the potentially serious forms of tuberculosis becomes an important but difficult one. Obviously, to advocate chemotherapy in such cases would be a new departure and would require prolonged treatment of vast numbers of apparently healthy children, and perhaps the majority of certain populations, in the hope of preventing a small number of severe and potentially fatal complications. This type of approach has nevertheless been proposed recently by Dr. Edith M. Lincoln.*

In a recent report she presented data concerning the effects of antimicrobial therapy on the prognosis of primary pulmonary tuberculosis in children at Bellevue Hospital, where a careful study of such cases has been in progress since 1930. During the period 1930-1946 the mortality among 980 children with positive tuberculin tests and positive x-ray signs of pulmonary involvement but without calcification — that is, primary, active cases — admitted to the pediatric wards of Bellevue Hospital was 21.5 per cent. The deaths in 90 per cent occurred within the first year after the diagnosis was made. The cause of death in 60 per cent was meningitis; in an additional 10 per cent it was acute miliary tuberculosis without meningitis, and in the rest, constituting all but 5 per cent of the deaths, it was either a more protracted generalized hematogenous form or a locally progressive primary pulmonary disease with cavitation and bronchogenic spread.

Chemotherapy with streptomycin, combined with either para-aminosalicylic acid (PAS) or a sulfone, Promizole (used in meningitis and apparently advocated now only rarely by others than Dr. Lincoln), was used from 1947 to 1951. This treatment, however, was limited to about 35 per cent of the cases — namely, patients who were suspected of having the types of complications that accounted for the deaths in the earlier period. The mortality in the total group of 421 patients observed during the second period was only 5 per cent. In the third period, 1952-1953, isoniazid was added to the combination of streptomycin with either PAS or Promizole, and the mortality in 129 patients observed during this period

*Lincoln, E. M. Effect of antimicrobial therapy on prognosis of primary tuberculosis in childhood. *Am. Rev. Tuberc.* **69**:682-689, 1954.

was 1.5 per cent, again only the potentially serious cases being treated. The condition of an appreciable proportion of the survivors among those with meningitis left something to be desired. Several of them had severe neurologic and mental impairment, and about a third suffered either diminution or loss of hearing.

In the cases of meningitis the results seemed to depend on the stage of the disease when treatment was started; among those treated in the earliest stage 85 per cent survived as compared with 77 per cent treated in the second stage and only 31 per cent treated late in the disease. The immediate prognosis in the patients with a primary pulmonary focus was good so far as local progression of the lesion was concerned. The protracted hematogenous form had previously resulted in death within six months, and the survivors frequently showed relapses; under chemotherapy the early deaths were prevented, and the disease was rendered inactive so that relapses were not encountered. In cases of extensive tuberculous bronchopneumonia the disease apparently showed complete regression under treatment in most cases, and some patients with residual cavitation were helped by surgical resection of the cavitary foci. Streptomycin, with the addition of either PAS or a sulfone, produced rapid improvement in cases of tuberculous laryngitis and in those with cutaneous sinuses; in the latter such treatment permitted surgical procedures, which resulted in further improvement in the disease. Chemotherapy has also been very useful as a preoperative and postoperative adjunct and has improved the prognosis in the surgical treatment of focal lesions. However, in bone and lymph-node tuberculosis, the results have been difficult to evaluate, and in cases of endobronchial tuberculosis there seemed to be little or no effect on the symptoms or course of the disease.

The addition of isoniazid has had some interesting effects. In the first place it has improved the survival rate in cases of meningitis. Secondly, it has made possible a reduction in the dose of streptomycin, after the fourth or sixth week of treatment, so that injections of streptomycin can be given twice weekly instead of daily. The use of streptomycin intrathecally has also been abandoned when isoniazid is used. As a result of these changes deafness has not been encountered in cases of meningitis since the introduction of isoniazid and the changed streptomycin regimen. Thirdly, the results in miliary tuberculosis have been excellent, even when isoniazid has been given without streptomycin; in the hematogenous forms cures have been obtained, and the development of clinical manifestations of meningitis has been prevented. Apparently, other observers have noted the failure of meningitis to develop in any of their patients under treatment with isoniazid for any form of tuberculosis. In patients previously treated with streptomycin alone, and even with the addition of PAS, meningitis frequently occurred during treatment for miliary tuberculosis.

The great majority of cases, including two thirds of all the ward patients admitted to Bellevue Hospital, however, have asymptomatic primary disease. In these cases no treatment had been given, for various reasons. In the first place there was no evidence that treatment resulted in a more rapid resolution of the primary pulmonary focus. Secondly, complications in bones, lymph nodes and other areas had been observed to develop and progress under streptomycin treatment given for other forms, and, when isoniazid was not used, meningitis often developed in patients under treatment for miliary tuberculosis. Thirdly, the possibility of the emergence of resistant forms of tubercle bacilli had to be considered since this renders the treatment of subsequent complications ineffective, and even when such resistant organisms are not demonstrable, retreatment is usually less effective at a later date. Isoniazid seemed to overcome some of these difficulties, and although there was no evidence of a faster resolution of primary lesions, the prognosis was improved because meningitis did not develop in patients under treatment with isoniazid, even when tubercle bacilli were found in the cerebrospinal fluid.

Dr. Lincoln has taken these findings as a challenge and as a reason to consider the possibility of changing the indications for chemotherapy in the primary tuberculous complex. She now raises a question whether chemotherapy should not be considered for every child with active tuberculosis, and probably also for children with known conversion of the tuberculin test even if the x-ray picture is normal. Under these conditions treatment would be necessary for one year to cover the period when clinical meningitis might develop. Since the proof of the effectiveness of such therapy would depend on its use on a huge scale, Dr. Lincoln proposes a carefully controlled study in many large clinics throughout the country.

Before such a project is undertaken, however, certain other aspects of the problem must be considered. If one proposes to treat all patients as soon as they are found to convert from negative to positive tuberculin reactors, there is a possibility that many of them will again give a negative tuberculin test; such children would then be about as susceptible as they were before treatment was started. Since their sources of infection are not eradicated, they may be equally susceptible and may again have to be treated when the signs of primary or slightly modified disease develop. The wisdom of such a regimen might also be called into question when the mortality in the active primary disease has been reduced from 21.5 to 1.5 per cent, and particularly when the deaths that do occur seem to be limited almost entirely to late and neglected cases. Would it not, therefore, be better and more effective to set up a case-finding and follow-up program to detect cases early, and then to

limit treatment to those with early active disease of the type that is likely to be serious and at the same time seek out and attempt to reduce the source of these infections? This seems to be a generally more practical approach, and one that would not subject the great majority of the young population to a long, serious and tedious type of treatment but would still accomplish the major objective of reducing the mortality and morbidity from this disease.

REHABILITATION FOR INDEPENDENCE

BEGINNING Tuesday, November 2, and continuing through November 6, the National Society for Crippled Children and Adults will hold its thirty-first national convention in Boston, the Bay State Society for the Crippled and Handicapped serving as host.

More than 1000 delegates, representing 1200 Easter Seal Societies, all affiliates of the National Society, are expected to take part in the five-day program of panels, lectures, and discussion focusing on the theme "Rehabilitation for Independence."

Since this is the first time the National Society has ventured farther east than New York City for one of its annual sessions, the *Journal* extends a hearty and cordial New England welcome and proffers its best wishes for progress, knowing that Boston and its wealth of talent has much to offer those dedicated to the work of rehabilitating the whole person for participation in everyday life at home, school, work and play.

RED FEATHER CAMPAIGN

A KNOWLEDGE of various facts is necessary for an appreciation of the annual Red Feather Campaign of Metropolitan Boston for 1955, which will be inaugurated this year on October 24 to continue through November 23. It should be recalled that this will be, paradoxically, the twentieth annual campaign to be prosecuted in this area, to support nearly 300 health and social welfare services in approximately 48 metropolitan communities. The paradoxical situation is that the first of the twenty annual campaigns took place nineteen years ago, in 1936.

Largely because of the fact that over 30,000 volunteers will engage in the solicitation of contributions, the cost of this undertaking will amount to only 5½ cents on the dollar; the goal has been set at $6,550,000, or barely $200,000 more than was raised last year. The figure represents only about $3.00 per capita of the population of the area.

The services that receive part of their support from the Red Feather funds include 23 neighborhood houses, 9 Boy Scout and 4 Girl Scout councils and 2 councils of Camp Fire girls. Twenty-seven hospitals receive aid from this source, United Community Services providing more than 1,000,000 days of hospital care. Three child-guidance clinics and 4 agencies for the help of homeless children are also partly supported as a result of this tremendous effort to organize the sometimes haphazard generosity of that segment of the population that has developed a true social consciousness.

Despite these efforts at organization, the success of the Red Feather appeal is annually jeopardized by the steadily increasing host of agencies that make an independent solicitation. The best advice that can be offered to the recipient of these pleas is to support to the limit his community chest and those charities in which he has a special interest. Otherwise, his dollar for benevolences will be sliced as by a microtome.

Good openings for medical men are ready for occupancy both in Nebraska and Kansas. This is the proper time for going to those countries.

Boston M. & S. J., *Oct. 25, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

AVERILL — George G. Averill, M.D., of Waterville, Maine, and formerly of Cambridge, died on September 19. He was in his eighty-fifth year.

Dr. Averill received his degree from the College of Physicians and Surgeons, Boston, in 1892.

YOUNG — Walter H. Young, M.D., of Dedham, died on September 18. He was in his seventy-eighth year.

Dr. Young received his degree from Tufts College Medical School in 1907. He was an associate fellow of the American Medical Association and formerly a member of the staffs of the Norwood, Needham, Newton–Wellesley and Faulkner hospitals and the Massachusetts Eye and Ear Infirmary.

He is survived by his widow.

BOSTON MEDICAL LIBRARY

RECENT ACCESSIONS OF UNUSUAL INTEREST

The following sixteenth-century works were recently acquired by the Library:

Berengarius de Carpi. *Tractatus perutilis et completus de fractura cranei* (Venice: J. A. de Nicolinis de Sabio, 1535). The Library also has his anatomy, *Isagogae breves plucide ac uberrime, in anatomia humani corporis* (Bologna: Benedictus Hectoris, 1523).

Champier, Symphorien. *Le questionaire des cirurgiens et barbiers* (Paris: 1533). This unusual book

is in the vernacular; most works of Champier were written and printed in Latin. The Library has an important collection of this physician, totaling 30 titles and with the other editions forming 36 books in all. The *Questionaire* is the only one in French.

Lullus, Raymundus [Lull, Ramon]. *Ars magna, generalis et ultima* (Lyon: Jacobus Marechal, 1517). This is the first edition with the triple rotary figure complete. This book may be considered a companion work to the author's *Arbor scientia,* of which the Library has the editions of Barcelona (1482) and Lyon (1515). The small but important collection of Lullus now numbers 9 volumes, 3 of the fifteenth and 6 of the sixteenth centuries.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date		Clinic Consultant
Salem	November	1	Paul W. Hugenberger, M.D.
Gardner	November	2	Carter R. Rowe, M.D.
Greenfield	November	4	Charles L. Sturdevant, M.D.
Lynn*	November	8	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Haverhill	November	10	William T. Green, M.D.
Lowell	November	12	Albert H. Brewster, M.D.
Pittsfield	November	17	Edward J. Coughlin, Jr., M.D.
Brockton	November	18	George W. Van Gorder, M.D.
Hyannis	November	18	Paul L. Norton, M.D.
Worcester	November	19	John W. O'Meara, M.D.
Fall River	November	22	David S. Grice, M.D.
Springfield	November	23	James B. Fisher, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	November 2, 9, 16, 23, 30
Fitchburg	November 3, 10, 17, 24

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett, and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

ET TU, R. I.

To the Editor: Although Rhode Island may be the smallest state in the Union, its citizens are very proud of it. It is that which leads me to write this letter pointing out a slight —unintentional, I know—to our fair state.

Sievers, in his article entitled "An Unusual Case of Sporotrichosis," which appeared in the May 13 issue of the *Journal,* made the statement that only 8 cases of sporotrichosis have been reported from the New England area. He went on to report that, of these, 4 were from Connecticut, 2 from Massachusetts and 1 each from Maine and New Hampshire.

I should like to respectfully call attention to the fact that Rhode Island may justly join its neighbors in the listing since Schiff, in an article on the subject "Solitary Sporotrichotic Granuloma" (*Arch. Dermat. & Syph.* 65:353-355, 1952) reported a case of sporotrichosis in a Rhode Island farmer.

Arthur B. Kern, M.D.

Providence, Rhode Island

PURIST DEPRECATES PURULENT PUS

To the Editor: An enema is "a fluid injected into the rectum for the purpose of clearing out the bowels, or of administering drugs or food."

An enema is *not* a period of time; ergo, *no* "perforations during enemas!" (*New Eng. J. Med.* 251:308, 1954). Such language from Boston and the Massachusetts General! I have a hard time trying to get the medical grammar of Boston back to a state of respectability, to say nothing of a state deserving of emulation.

Old Village Doctor

In "Uncultured" North Carolina

P.S. And in the same issue (p. 315) "purulent pus." May the Lord save us!

Note: "During," as Mr. Webster also reminds us, is a preposition expressive of time. It is not, however, necessarily associated only with nouns denoting time but also with those of actions, events or states that occur within the limits of time. Thus, during life, during the battle, the race or whatnot need not be considered as incorrect. Many persons may justly think of an enema as an event, in which the *Century Dictionary,* Billings and other medical dictionaries concur, and during it many things happen, including perforations. The Editor disagrees with the Village Doctor that "during enemas" is carrying word saving to an unwholesome extreme but shares with the correspondent from North Carolina his amazement at "purulent pus," however euphonious.—Ed.

BOOK REVIEWS

Epilepsy and the Functional Anatomy of the Human Brain. By Wilder Penfield, O.M., C.M.G., M.D. (Johns Hopkins), B. Litt. and D.Sc. (Princeton), B.Sc., and D.Sc. (Oxon.), F.R.C.S., F.R.S.; and Herbert Jasper, M.D., C.M. (McGill). 8°, cloth, 896 pp., with 314 illustrations and 8 color plates. Boston: Little, Brown and Company, 1954. $16.00.

This beautiful volume of 896 pages marks an epoch in the study of epilepsy, reporting a quarter of a century of work at the Montreal Neurological Institute by Penfield and his colleagues. Jasper, who wrote a third of the book, has spent years in studying the pathological physiology of epilepsy, primarily by means of the electroencephalogram. In 1941 Penfield and Erickson presented a book, *Epilepsy and Cerebral Localization,* which covered research on epilepsy from the surgical point of view up to that date. The present volume is so much more comprehensive and has so much new material that it can in no way be considered a second edition of that work.

Especially noteworthy are the chapters on anatomy and physiology, which co-ordinate the observations of the authors and show how much the study of epilepsy has contributed to the understanding of the physiology of the brain. Localization of cerebral function has been greatly elucidated by the operations on the human brain under local anesthesia. No experiments on animals can approach in importance the authors' observations. As Sherrington once said to Penfield, "It must be great fun to ask the 'preparation' a question and have it answer you."

The sixth through thirteenth chapters are no less important, describing in unique detail the clinical phenomena of epilepsy as observed at the bedside, in the electroencephalographic laboratory and in the operating room. The seventh deals with the pathology of the epileptogenic lesions. Medical treatment is discussed by McNaughton in the fourteenth chapter. The last 5 chapters contain discussions of special technics, such as surgical excision of lesions, electrocorticography of the exposed brain and x-ray study.

One of the most remarkable observations made by Penfield is that "psychical hallucinations" can be elicited by electric stimulation of the temporal lobe of some epileptic patients:

> . . . such hallucinations, or memories, or dreams continue to unfold slowly while the electrode is held in place. They are terminated suddenly when the electrode is withdrawn. This is a startling discovery. It brings psychical phenomena into the field of physiology.

This certainly is a discovery, since it is an entirely new observation and has important implications for psychology. Until Penfield's patients told of these vivid recollections, resembling dreams because whole scenes were seen and heard, cortical stimulation had produced only crude and abnormal sensations. To this reviewer the discovery is exciting but not startling. Somehow, Penfield hit upon an adequate stimulus; applied in this area, it would, one would expect, provoke complex reactions because the temporal lobe is a crossroads where archicortex and neocortex come close together and where one expects vision, hearing, emotion and visceral reactions to be integrated. Penfield says, "The permanent record of experience is to be found in the connecting pattern of neurones in the temporal cortex." Perhaps it would be safer to say "a permanent record," because if the normal adequate stimulus could be applied to parts of the frontal and parietal areas it seems probable that there also a permanent record of experience would be found.

The most controversial statement in the book is that the "highest level of neuronal integration must be sought in the diencephalon and midbrain." This brings up Penfield's new conception of a "centrencephalic integrating system" or "area of final integration" in the upper brain stem. The evidence for this is impressive and fits in with some recent theories of cerebral function. But it will take more research and careful judgment before the relations between cortex and thalamus are clearly understood.

STANLEY COBB, M.D.

Planning Guide for Radiologic Installations. By the Committee on Planning of Radiologic Installations of the Commission on Public Relations of the American College of Radiology. Wendell G. Scott, M.D., chairman. 4°, cloth, 336 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1953.

The information in this publication has been acquired with the assistance of a large group of individual contributors, the various companies manufacturing x-ray equipment and film, federal health agencies, the American Hospital Association and the American Institute of Architects, all collated and correlated under the direction of the American College of Radiology. As set down in the introduction and statement of purposes, the book is intended to "Assemble all available information related to design, construction, or remodeling . . . to embody chapters expressing the viewpoints of all interested groups . . . not to be an ideal drawing for a contractor . . . but to present a suggested or desirable list of recommended arrangements as to space, design, features, function and protection. . . ."

The volume well satisfies these criteria. The 22 chapters and 3 appendixes cover all individual subheadings of planning from film processing, facilities and filing, through radiation protection, mobile equipment and so forth to dressing booths, decoration, air conditioning and architectural problems. Individual consideration is given to problems of hospital and private office, of radioisotope and radium handling and many others. The wealth of detail is considerable, and in almost every instance several different methods or arrangements are presented as alternate ways of handling specific problems.

Probably even greater service than the collection of answers, however, is rendered by the presentation of the problems themselves. Careful reference to this volume should obviate most errors of omission that might result from failure to recognize or remember the existence of some particular problem that must be allowed for in the course of planning any radiologic installation whether the method used is one of those suggested or an entirely different one. In this respect alone the volume should prove extremely valuable whenever radiologic planning is undertaken, and it is recommended particularly to radiologists, directors of hospitals, research institutions and medical schools, as well as the architects working in these fields.

J. LELAND SOSMAN, M.D.

Aggression, Hostility and Anxiety in Children. By Lauretta Bender, M.D., professor of clinical psychiatry, New York University College of Medicine, associate attending psychiatrist, New York University-Bellevue Medical Center, and senior psychiatrist in charge of Children's Service of the Psychiatric Division, Bellevue Hospital, New York City. 4°, cloth, 184 pp., with 13 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $5.50.

Once upon a time, as the fairy tales say, children were supposed to be good little children. It is still desirable, but in a world containing hydrogen bombs, "miracle drugs," psychoanalysis, the theory of organic evolution, relativity and socialists, things have changed vastly from grandmother's day. This book is the second in a series dealing intensively with children. It is remarkably objective and deals with practical problems that have come, day by day, into the Psychiatric Clinic of Bellevue Hospital, where Dr. Bender works. A notable array of assisting talent contributed substantially to parts of the studies. Anyone interested in suicide, homicide, pyromania and other symptoms in children suffering with anxiety, hostility and other primitive disturbances will find this book of permanent value. It is beautifully printed and has a carefully prepared bibliography and index that make all parts of it immediately accessible to the physician, social worker and student of human nature.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Megaloblastic Anaemias. By L. J. Davis, M.D., F.R.C.P., F.R.C.P.E., F.R.F.P.S.G., F.R.S.E., Muirhead Professor of Medicine, University of Glasgow, and physician, Royal Infirmary, Glasgow; and Alexander Brown, M.D., F.R.C.P.E., F.R.F.P.S.G., senior lecturer in medicine in the University of Glasgow, and assistant physician, Royal Infirmary, Glasgow. 8°, cloth, 113 pp., with 12 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $4.50. (Publication No. 222, *American Lecture Series.*)

In this small monograph the author presents a survey of the literature on megaloblastic anemias. He discusses concepts of megaloblastosis, therapeutic preparations, pernicious anemia, megaloblastic anemia from intestinal dysfunction and diagnosis of megaloblastic anemia. There is a bibliography of 278 references and an index. The book was printed in England.

Digital Plethysmography: Introducing a method for recording simultaneously the time course of the rate of blood flow into and out of the finger tip. By George E. Burch, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University of Louisiana School of Medicine, physician-in-chief, Charity Hospital, consultant in cardiovascular disease, Ochsner Clinic, Hôtel Dieu and Mercy hospitals, and visiting physician, Touro Infirmary, New Orleans. 8°, cloth, 134 pp., with 84 illustrations. New York: Grune and Stratton, 1954. $5.00. (*Modern Medical Monographs* No. 11.)

This monograph is concerned primarily with recent experimental studies and the author's method of recording the rate of blood by digital plethysmography. There is a list of 27 references, as well as an index.

NONCLINICAL NOTES

INTERNATIONAL SOCIETY OF HEMATOLOGY

Dr. William Dameshek, of Boston, senior physician and hematologist at the New England Center Hospital and professor of clinical medicine at Tufts College Medical School, was elected president of the International Society of Hematology at the Society's congress in Paris in September.

NATIONAL MUSCULAR DYSTROPHY RESEARCH FOUNDATION

Mr. F.R.C. Brown, of the Texas Gulf Sulphur Company, has been appointed president of the National Muscular Dystrophy Research Foundation of Liberty, Texas.

The National Muscular Dystrophy Research Foundation has made grants totaling $6500 to the Southwest Foundation for Research and Education, of San Antonio, Texas, for a medical research project entitled "Individual Metabolic Patterns for Members of Families Having a History of Muscular Dystrophy" conducted and supervised by Drs. Roy B. Mefferd, Jr., and N. T. Werthessen.

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Dr. Mario Stefanini, formerly at the New England Center Hospital, became a member of the Department of Medicine, University of Louisville School of Medicine, on October 1.

MASSACHUSETTS SOCIETY FOR RESEARCH IN PSYCHIATRY

The Massachusetts Society for Research in Psychiatry announces the election of the following officers: Dr. Rudolph Kaldeck, president; Dr. Daniel H. Funkenstein, vice-president; and Dr. Max Rinkel, secretary-treasurer.

NEW ENGLAND HOSPITAL APPOINTMENT

Dr. M. Alice Phillips has been appointed chief of the Department of Obstetrics and Gynecology at the New England Hospital.

NOTICES

NEW ENGLAND DIABETES FAIR

The fifth annual Diabetes Fair, sponsored by the New England Diabetes Association, will be held on Tuesday and Wednesday, November 16 and 17, 1954, during National Diabetes Week, at Mechanics Building, Boston, from 11 a.m. to 10 p.m.

The purpose of the Fair is to educate and stimulate interest in the public concerning diabetes and its detection, and to urge the public at large to go to their family doctor and have a urine test for sugar and a blood test if necessary.

There will be exhibits illustrating various phases of diabetes and its management. These will include displays concerning pharmaceuticals, dietetics, social and public service aids, diabetes camps, insurance for diabetic persons, diabetes detection and nursing care in the hospital and at home. There will be books and pamphlets on diabetes and charts illustrating medical and surgical features of diabetes. Motion pictures will be presented. Owing to the public interest in the lectures and panel discussions last year, these will be held again in the afternoon and evening of both days featuring various aspects of diabetes.

X-ray films of the chest will be taken for those desiring them. Facilities will be provided for urine sugar and blood sugar testing, done chiefly as an educational procedure so that the public may see the methods. In addition nearly 100 new cases of diabetes have been found at each fair. However, as a result of experience in the past, blood sugar tests will be done only on persons showing glycosuria as a screening test for diabetes.

Physicians, medical students, nurses, social workers and the general public are invited to attend.

NEW ENGLAND DIABETES ASSOCIATION

A meeting of the New England Diabetes Association will be held in the Joslin Auditorium, New England Deaconess Hospital, Monday, November 1 at 8:15 p.m.

There will be a symposium on insulin. Drs. Claude A. Villee and William R. Kirtley will be the speakers. Interested physicians are invited.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

A symposium on office procedures in gynecology, proctology, urology, cardiology, child psychiatry and forensic medicine will be held under the auspices of the Springfield Regional Chapter of the Massachusetts Academy of General Practice at the Hotel Kimball, Springfield, Massachusetts, on November 17. All physicians and their families are invited to the luncheon and the cocktail party that will follow the lectures.

MASSACHUSETTS PHYSICIANS ART SOCIETY

A meeting of the Massachusetts Physicians Art Society will be held at the headquarters of the Massachusetts Medical Society, 22 Fenway, on Thursday, November 4, at 7:30 p.m.

All members and other interested physicians are invited.

MASSACHUSETTS HEART ASSOCIATION GRANTS

The Research Allocations Committee of the Massachusetts Heart Association is receiving requests from institutions for grants-in-aid for research in cardiovascular diseases. The Committee will meet as follows: November 18, January 28, March 25 and May 27. Applications should be received no less than fifteen days before a meeting. Further information may be obtained from Miss Margaret Taylor, Massachusetts Heart Association, 650 Beacon Street, Boston 15.

SYMPOSIUM ON CHRONIC PULMONARY DISEASE

A symposium on chronic pulmonary disease, sponsored by the Medical Society of the County of Queens, Queens County Chapter, Academy of General Practice, and the Queensboro Tuberculosis and Health Association, will be held in the building of the Medical Society of the County of Queens, 112-25 Queens Boulevard, Forest Hills, New York, on November 11, at 2 and 8 p.m. It is approved by the American Academy of General Practice for five hours of formal credit. Further information may be obtained from Miss Miriam Tauber, Queensboro Tuberculosis and Health Association, 159-29 90th Avenue, Jamaica, New York.

EXAMINATIONS FOR MEDICAL OFFICER

New examinations have been announced by the United States Civil Service Commission for filling medical-officer positions in Washington, D.C., and vicinity and the United States Public Health Service and Children's Bureau agencies throughout the United States and the Panama Canal Zone. Applications for positions in the agencies in the United States must be filed with the United States Civil Service Commission, Washington 25, D.C., and those for positions in the Panama Canal Zone with the Board of United States Civil Service Examiners, Balboa Heights, Canal Zone.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS FELLOWSHIPS

The National Foundation for Infantile Paralysis announces the availability of fellowships to psychiatrists interested in emotional problems of the patient with poliomyelitis in respiratory difficulty, postdoctoral fellowships in medi-

cine and related biologic sciences, clinical fellowships to physicians interested in rehabilitation as related to their particular specialties and clinical fellowships in physical medicine and rehabilitation.

Further information may be obtained from the National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5, New York.

INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA

The International Medical Assembly of the Interstate Postgraduate Medical Association of North America will be held in the municipal auditorium, Minneapolis, Minnesota, November 1-4.

AMERICAN COLLEGE OF CARDIOLOGY

The third interim scientific meeting of the American College of Cardiology will be held at the Hotel Algiers, Miami Beach, Florida, November 11 through 13.

There will be four scientific sessions on the topic "Diet in Heart Disease." Further information may be obtained from the secretary, Dr. Philip Reichert, 140 West 57th Street, New York 19, New York.

POSITION AT REDSTONE ARSENAL

Two medical officers are needed at Redstone Arsenal, Huntsville, Alabama, at salaries of $7040 and $8360 per year, respectively. Application may be made on Standard Form 57 (application for federal employment) to the Civilian Personnel Officer, Redstone Arsenal, Huntsville, Alabama, attention of Miss Dorothy Hodges.

SOCIETY MEETINGS AND CONFERENCES

October, 1954–April, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

October 25. Massachusetts Heart Association Kidney Section. Page 631, issue of October 7.

October 25–27. New England Postgraduate Assembly. Hotel Statler, Boston. Page xvi, Advertising Section.

October 25–27. National Gastroenterological Association. Page 496, issue of September 16.

October 25, 27 and 29. Edward K. Dunham Lectures. Page 679, issue of October 14.

October 25–28. Consultation Clinics for Crippled Children in Massachusetts. Page 586, issue of September 30.

October 25–December 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

October 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.

October 27. Massachusetts Society of Examining Physicians. Page 679, issue of October 14.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

October 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.

October 27, December 1, February 4 and April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

October 29. Massachusetts Public Health Association. Fall Meeting. Blake's Restaurant, Springfield, Massachusetts.

October 30. Massachusetts Association of Medical Technologists. Page 679, issue of October 14.

October 31. Medical Television Program. March of Medicine. Page 631, issue of October 7.

October 31–November 4. American Institute of Dental Medicine. Page 968, issue of June 3.

November, 1954–May, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

November 1, 1954–January 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

November 1. New England Diabetes Association. Page 721.

November 1–4. Interstate Postgraduate Medical Association of North America. Notice above.

November 2–5. Fourth Annual Bay State Rehabilitation Conference. Hotel Statler, Boston.

November 2–6. National Society for Crippled Children and Adults. Page 631, issue of October 7.

November 3 and 4. M & R Pediatric Research Conference. Page 496, issue of September 16.

November 4. Massachusetts Physicians Art Society. Page 721.

November 6. Massachusetts Hospital School Symposium. Page 495, issue of September 16.

November 11. Symposium on Chronic Pulmonary Disease. Page 721.

November 11–13. American College of Cardiology. Notice above.

November 12. Memorial Center for Cancer and Allied Diseases Conference. Page 544, issue of September 23.

November 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

November 15–19. American College of Surgeons. Page 496, issue of September 16.

November 15–26. Laboratory Diagnosis of Tuberculosis Course. Page 246, issue of August 5.

November 16 and 17. New England Diabetes Fair. Page 721.

November 17. American Trudeau Society. Page 588, issue of September 30.

November 17. Massachusetts Academy of General Practice. Page 721.

November 29–December 1. Association of Military Surgeons of the United States. Page 631, issue of October 7.

December 3, 1954; February 4 and April 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

December 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

December 7. Medical Television Program. The Doctor. (Cavalcade of America.) Page 631, issue of October 7.

December 8. New England Pediatric Society. Page 968, issue of June 3.

December 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

January 3–May 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

January 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

February 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.

February 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

March 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 28

THURSDAY, OCTOBER 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. Esophageal Neoplasms and Diverticula. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Observations on the Acute Allergic Reactions Induced by the Injection of Allergenic Extracts. Dr. Francis C. Lowell. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, OCTOBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
5:00 p.m. Edward K. Dunham Lecture. Building C, Harvard Medical School, 25 Shattuck Street.

SATURDAY, OCTOBER 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
9:30 a.m. Massachusetts Association of Medical Technologists. Beverly Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xxiv)

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Program

MONDAY, OCTOBER 25, 1954

MORNING SESSION

MOTION PICTURES — *Ball Room Assembly*

8:30 Acute laryngotracheo-bronchitis. (The Children's Hospital, Montreal.)
Discusser: DR. CHARLES A. JANEWAY

8:50 Discussion and Coffee Break.

SYMPOSIA — *Georgian Room*

9:20 (1) Problems in Industrial Medicine Confronting the Practitioner.
Moderator: DR. JOSEPH C. AUB, DR. WILLIAM DAMESHEK, DR. JOHN G. DOWNING, DR. HARRIET L. HARDY.

Ball Room Assembly

9:20 (2) Correctable Congenital Cardiac Disease.
Moderator: DR. GORDON S. MYERS; DR. ALEXANDER S. NADAS, DR. J. GORDON SCANNELL.

LECTURES — *Georgian Room*

10:40 The Diagnosis and Management of Biliary Tract Disease.
DR. ROBERT M. ZOLLINGER, Columbus, Ohio.

11:15 Pancreatitis.
DR. FRANZ J. INGELFINGER

11:50 Discussion.

LUNCHEON PANELS — *No. 1 — Parlor A*

12:20 Surgery in the Ulcer Problem.
Moderator: DR. FRANZ J. INGELFINGER; DR. FRANCIS D. MOORE, DR. ROBERT M. ZOLLINGER.

No. 2 — Parlors B and C

12:20 Amenorrhea and Ovulation.
Moderator: DR. JOHN ROCK; DR. JANET W. MCARTHUR, DR. SOMERS H. STURGIS.

AFTERNOON SESSION

LECTURES — *Georgian Room*

2:35 The Present Scope of Radio-Isotope Therapy.
DR. SHIELDS WARREN

3:05 Radio-Isotopes in a Community Hospital.
DR. JOHN W. TURNER

3:30 Discussion.

4:00 Application of Recent Nutrition Researches to Specific Medical Problems of General Practice.
DR. FREDERICK J. STARE; DR. THOMAS R. A. DAVIS, DR. WILLIAM R. WADDELL.

5:15 COCKTAIL PARTY

TUESDAY, OCTOBER 26, 1954

MORNING SESSION

MOTION PICTURES — *Ball Room Assembly*

8:30 Function of the Mitral Valve in Situ. (Montefiore Hospital, New York.)
Observations on the Aortic Valve.
(Dr. MacMillan, Leeds, England.)
Discusser: DR. JAMES H. CURRENS

8:50 Discussion and Coffee Break.

SYMPOSIA — *Georgian Room*

9:20 (1) Traumatic Neurosis as a Compensation Problem.
Moderator: DR. GEORGE A. MARKS; MR. EUGENE GIROUX, DR. ALEXANDER P. AITKEN, DR. HERBERT BARRY, JR.

Ball Room Assembly

9:20 (2) Diverticulosis and Diverticulitis.
Moderator: DR. MARSHALL K. BARTLETT; DR. BENJAMIN M. BANKS, DR. JAMES R. LINGLEY.

LECTURES — *Georgian Room*

10:40 Problems in Adolescence.
DR. J. ROSWELL GALLAGHER

11:15 Surgical Pitfalls in the Psychoneurotic.
DR. CHESTER M. JONES

11:50 Discussion.

LUNCHEON PANELS — *No. 3 — Parlor A*

12:20 Hiatus Hernia, Esophagitis and Angina.
Moderator: DR. PERRY J. CULVER; DR. RICHARD SCHATZKI, DR. RICHARD H. SWEET.

12:20 *No. 4* — Juvenile Delinquency.
Moderator: DR. J. ROSWELL GALLAGHER, MR. FRED B. TAYLOR.

AFTERNOON SESSION

LECTURES — *Georgian Room*

2:35 Lessons Learned from the Worcester Tornado.
DR. DONALD HIGHT

3:00 Public Health Aspects of the Worcester Tornado, 1953.
DR. SAMUEL B. KIRKWOOD

3:30 Management of the Acutely Injured.
DR. THOMAS B. QUIGLEY

4:00 Discussion.

4:30 CLINICAL PATHOLOGICAL CONFERENCE
Chairman: DR. WILLIAM A. MEISSNER
Discussers: DR. DONALD E. BROWN; DR. STANLEY L. ROBBINS, DR. SHELDON C. SOMMERS.

EVENING SESSION

JAMBOREE — *Georgian Room*

8:15 Miraculous Escapes of a Secret Agent.
MAJOR ARIE D. BESTEBREURTJE
Romantic Interludes.
HERB AND BETTY WARNER

WEDNESDAY, OCTOBER 27, 1954

MORNING SESSION

MOTION PICTURE — *Ball Room Assembly*

8:30 Observation of Human Ovulation by the Pelviscope. (Dr. Joseph Doyle)
Discusser: DR. FRED A. SIMMONS

8:50 Discussion and Coffee Break.

SYMPOSIA — *Georgian Room*

9:20 (1) The Unconscious Patient.
Moderator: DR. JOSEPH M. FOLEY; DR. C. MILLER FISHER, DR. ARNOLD S. RELMAN, DR. BERTRAM SELVERSTONE.

Ball Room Assembly

9:20 (2) Problems in Thyroid Disease.
Moderator: DR. EARLE M. CHAPMAN; DR. BENTLEY P. COLCOCK, DR. A. S. FREEDBERG, DR. SIDNEY H. INGBAR.

LECTURES — *Georgian Room*

10:40 Antibiotic Therapy.
DR. YALE KNEELAND, JR., New York City.

11:15 Chemo-Prophylaxis.
DR. LOUIS WEINSTEIN

11:50 Discussion.

LUNCHEON PANELS — *No. 5 — Parlors B and C*

12:20 Office Management of Diabetes Mellitus.
Moderator: DR. W. RICHARD OHLER; DR. ALLAN M. BUTLER, DR. DAVID HURWITZ, DR. ALEXANDER MARBLE.

No. 6 — Parlor A

12:20 Anemia.
Moderator: DR. WILLIAM B. CASTLE; DR. LOUIS K. DIAMOND, DR. CHARLES P. EMERSON.

LECTURES— *Georgian Room*

2:35 Pregnancy and Heart Disease.
DR. C. SIDNEY BURWELL

3:00 Metabolic Bone Diseases; Osteoporosis, Osteomalacia and Osteitis.
DR. PHILIP H. HENNEMAN

3:40 Cystocele and Prolapse.
DR. HOWARD ULFELDER

4:05 Discussion.

4:15 CLINICAL PATHOLOGICAL CONFERENCE
Chairman: DR. WILLIAM A. MEISSNER
Discussers: DR. YALE KNEELAND, JR., DR. LOUIS WEINSTEIN.

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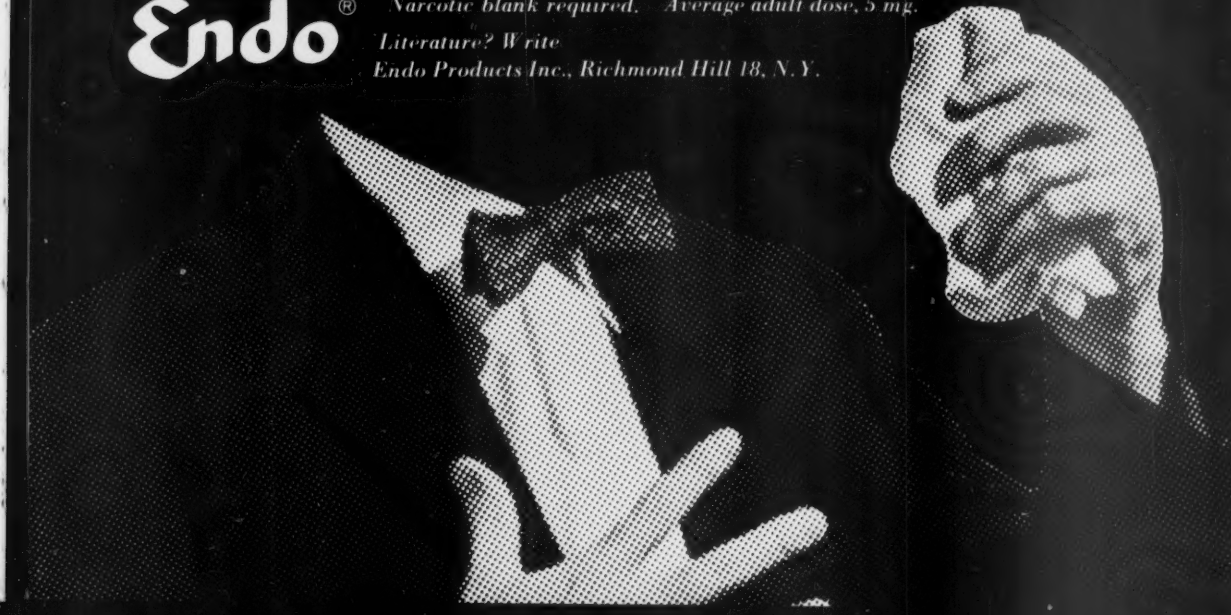

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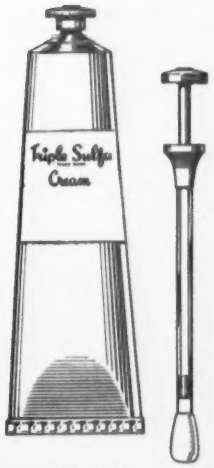

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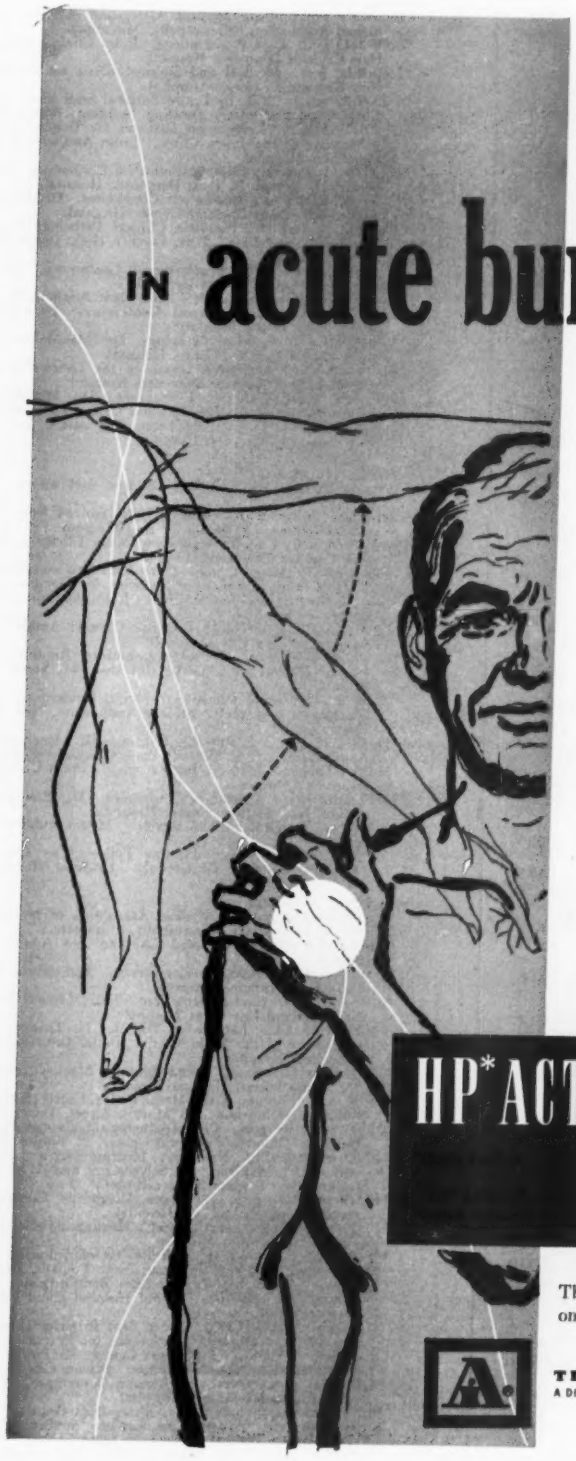

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NOTICES *(Concluded from page 722)*

MONDAY, NOVEMBER 1

Interstate Postgraduate Medical Association of North America. Municipal Auditorium, Minneapolis, Minnesota.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinical Pathology Conference. Drs. MacMahon and Baty. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.
*8:15 p.m. New England Diabetes Association. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, NOVEMBER 2

National Society for Crippled Children and Adults. Hotel Statler, Boston.
Interstate Postgraduate Medical Association of North America. Municipal Auditorium, Minneapolis, Minnesota.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:00 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Combined Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Drs. Patterson, MacMahon and guest. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic, New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, NOVEMBER 3

Interstate Postgraduate Medical Association of North America. Municipal Auditorium, Minneapolis, Minnesota.
National Society for Crippled Children and Adults. Hotel Statler, Boston.
M & R Pediatric Research Conference. Auditorium, State University College of Medicine, Syracuse.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th floor teaching unit, Beth Israel Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:00–9:00 p.m. Postgraduate Seminar in Pediatric Neurology and Psychiatry. Walter E. Fernald State School, Waltham.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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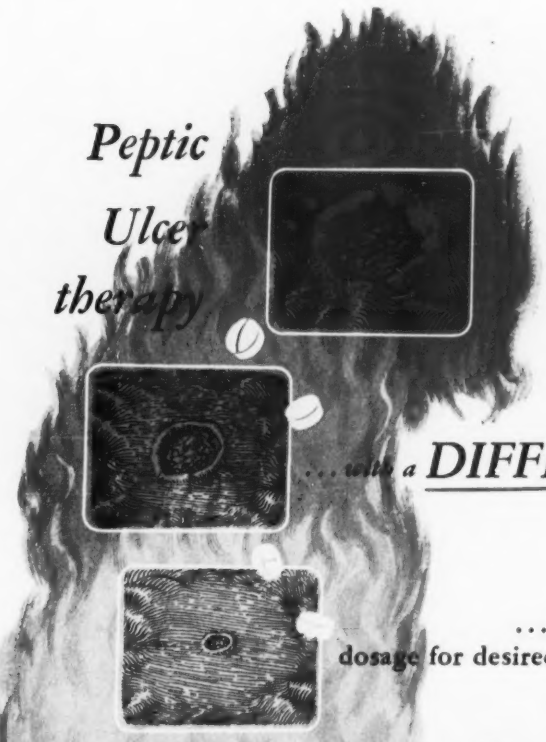

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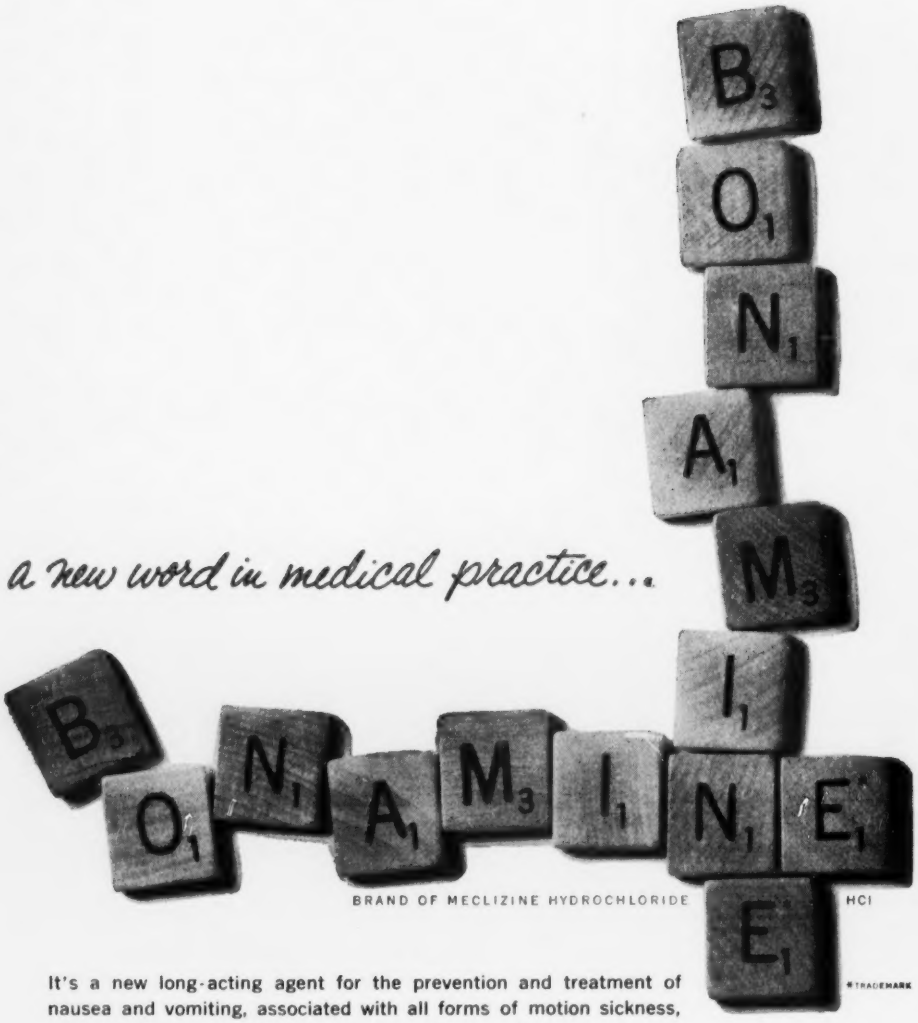

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